Medicines Management Programme

Managed Access Protocol – Medicines used in hereditary transthyretin amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy

Medicine	Date of addition to Managed Access Protocol
Patisiran (Onpattro®)	30/09/2021
Inotersen (Tegsedi®)	28/09/2022
Vutrisiran (Amvuttra®)	07/05/2024

Approved by	Professor Michael Barry, Clinical Lead, Medicines Management Programme.	
Date approved (patisiran):	Version 1.0	30/09/2021
Date approved (inotersen):	Version 1.0	28/09/2022
Date updated (patisiran, inotersen, vutrisiran combined):	Version 2.0	22/05/2024

Table of Contents

List of Tables

List of Abbreviations

ASO	Antisense oligonucleotide
BNP	B-type natriuretic peptide
ECHO	Echocardiography
FAP	Familial amyloidotic polyneuropathy
GalNAc	N-acetylgalactosamine
HSE	Health Service Executive
hATTR	Hereditary transthyretin (amyloidosis)
HTH	High Tech Hub
IV	Intravenous
MAP	Managed Access Protocol
MMP	Medicines Management Programme
2'-MOE	2'-O-2-methoxyethyl
mRNA	Messenger RNA
NICE	National Institute for Health and Care Excellence
NYHA	New York Heart Association
NT-proBNP	N-terminal pro b-type natriuretic peptide
PCRS	Primary Care Reimbursement Service
PFS	Pre-filled syringe
PND	Polyneuropathy disability
RNAi	Ribonucleic acid interference
SC	Subcutaneous
siRNA	Small interfering ribonucleic acid
SmPC	Summary of product characteristics
SOBI	Swedish Orphan Biovitrum Ltd
TSH	Thyroid stimulating hormone
TTR	Transthyretin

1. Treatments used in hereditary transthyretin amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy

The HSE has approved reimbursement of three medicines used in hereditary transthyretin (hATTR) amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy. Patisiran (Onpattro®) and vutrisiran (Amvuttra®) are available under hospital pricing approval and inotersen (Tegsedi®) is available under the High Tech Arrangement.

i. Patisiran (Onpattro®) is a double-stranded small interfering ribonucleic acid (siRNA) that specifically targets a genetically conserved sequence in the 3' untranslated region of all mutant and wild-type transthyretin (TTR) messenger RNA (mRNA). Patisiran is formulated as lipid nanoparticles to deliver the siRNA to hepatocytes, the primary source of TTR protein in the circulation. Through a natural process called RNA interference (RNAi), patisiran causes the catalytic degradation of TTR mRNA in the liver, resulting in a reduction of serum TTR protein.

From October 2021, one presentation of patisiran is available under hospital pricing approval:

- Onpattro® 2 mg/ml concentrate for solution for infusion (10 mg/5ml vial).

Each vial contains patisiran sodium equivalent to 10 mg patisiran formulated as lipid nanoparticles.

ii. Vutrisiran (Amvuttra®) is a chemically stabilised double-stranded siRNA that specifically targets variant and wild-type TTR 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 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.

From May 2024, one presentation of vutrisiran is available under hospital pricing approval:

- Amvuttra® 25 mg solution for injection in a prefilled syringe (PFS).

iii. Inotersen (Tegsedi®) is a 2'-O-2-methoxyethyl (2'-MOE) phosphorothioate antisense oligonucleotide (ASO) inhibitor of human TTR production. The selective binding of inotersen to the TTR mRNA causes the degradation of both mutant and wild type (normal) TTR mRNA. This prevents the synthesis of TTR protein in the liver, resulting in significant reductions in the levels of mutated and wild type TTR protein secreted by the liver into the circulation.

From October 2022, one presentation of inotersen is available under the High Tech Arrangement:

- Tegsedi® 284 mg solution for injection in a PFS.

1.1 Licensed indications

Patisiran (Onpattro®) and vutrisiran (Amvuttra®) are indicated for the treatment of hereditary transthyretin-mediated amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy.

Inotersen (Tegsedi®) is indicated for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis.

Please refer to the Summary of Product Characteristics (SmPC) for Onpattro® 2 mg/ml concentrate for solution for infusion, Amvuttra®25 mg solution for injection and Tegsedi® 284 mg solution for injection for full prescribing information.

1.2 Reimbursement

Reimbursement of patisiran and vutrisiran under hospital pricing approval, and inotersen under the High Tech Arrangement, is supported for adult patients who meet the criteria outlined in this MAP. All criteria must be satisfied in order for reimbursement to be supported.

An application for reimbursement approval is required to be submitted on an individual patient basis. The *Application form for Patisiran, Vutrisiran and Inotersen in hereditary transthyretin-mediated amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy* should be completed and sent by secure email to the HSE-Medicines Management Programme (MMP) at mmp@hse.ie. The drug treatment (patisiran, vutrisiran or inotersen) for which reimbursement approval is sought should be indicated on the application form at the time of application.

Table 1 outlines the licensed dosing of patisiran (Onpattro®), vutrisiran (Amvuttra®) and inotersen (Tegsedi®) in hATTR amyloidosis with stage 1 or stage 2 polyneuropathy.

Table 1: Licensed dosing of patisiran (Onpattro®), vutrisiran (Amvuttra®) and inotersen (Tegsedi®) in hATTR amyloidosis with stage 1 or stage 2 polyneuropathy

Medicine	Patient population	Route of administration	Dose
Patisiran	Adults < 100 kg	IV infusion	300 mcg per kg body weight once every three weeks
Patisiran	Adults ≥ 100 kg	IV infusion	30 mg once every three weeks
Vutrisiran	Adult patients	SC injection	25 mg once every three months
Inotersen	Adult patients	SC injection	284 mg once every week (on the same day each week)

IV: Intravenous, kg: kilogram, mcg: microgram, mg: milligram, sc: subcutaneous

Please refer to the SmPCs for more information on posology and method of administration. The SmPC for inotersen also contains information on dose adjustment in case of reduction in platelet count.

If a patient is recommended and approved for reimbursement of one of these medicines, reimbursement will be supported in line with the licensed doses as per the SmPCs i.e.

- for a maximum of three packs of patisiran (a total of 30 mg) every three weeks or
- for a maximum of one pack of vutrisiran (containing one PFS) every three months or
- for a maximum of one pack of inotersen (containing four PFSs) every four weeks

Reimbursement of these medicines is conditional on their use as monotherapy in hATTR amyloidosis with stage 1 or stage 2 polyneuropathy.

See Section 4 for further details on Reimbursement criteria - Medicines Management

1.3 Reimbursement price

The cost to the HSE of the available presentation(s) of these medicines is outlined in Tables 2 and 3.

Table 2: Ex-factory price of the presentation(s) of patisiran and vutrisiran available under hospital pricing approval

Strength (pack size)	Ex-factory price
Onpattro® 2 mg/ml concentrate for solution for infusion (1 x 5 ml vial)	€8,074.94^
Amvuttra® 25 mg solution for injection (1 x 25 mg/0.5 ml PFS)	€107,357.08

mg: milligram, ml: millilitre, PFS: pre-filled syringe, ^Correct as at 1st March 2024

Table 3: Reimbursement code and reimbursement price of the presentation of inotersen available under the High Tech Arrangement

	Reimbursement	
Strength (pack size)	**Code**	**Price**
Tegsedi® 284 mg solution for injection (4 x 1.5 ml PFS)	89227	€23,641.42^

mg: milligram, ml: millilitre, PFS: pre-filled syringe, ^Correct as at 1st March 2024

Based on the published ex-factory price (as set out in table 2 above) the annual treatment cost (including the framework agreement rebate and VAT at 23%) to maintain a patient using two vials of patisiran and three vials of patisiran every three weeks is approximately €320,000 and €480,000 respectively. Patients should be maintained on the lowest appropriate dose of patisiran.

Commercial in confidence arrangements are in place with the marketing authorisation holders to reduce the net acquisition cost of Onpattro®, Amvuttra® and Tegsedi® to the HSE.

2. Reimbursement criteria - Initiation

This section outlines the criteria that must be satisfied in order for an adult patient to be recommended for reimbursement of:

- patisiran or vutrisiran for the treatment of hATTR amyloidosis with stage 1 or stage 2 polyneuropathy under hospital pricing approval or
- inotersen for the treatment of stage 1 or stage 2 polyneuropathy with hATTR amyloidosis under the High Tech Arrangement.

2.1 Submission of Applications

Applications for reimbursement approval of patisiran, vutrisiran and inotersen will only be considered from consultants with experience in the diagnosis and management of hATTR amyloidosis in specialist centre(s) in Ireland, who are registered with the Irish Medical Council and have agreed to the terms of this managed access protocol (MAP) and have been approved by the HSE ('approved consultants').

Approved consultants are responsible for ensuring that the patient or their representative/guardian is aware that the application for reimbursement approval is being made on their behalf.

The prescribing of patisiran, vutrisiran and inotersen will be confined to the approved consultants and their teams. The governance of the team on the High Tech Hub (inotersen only), including access, rests with the approved consultant.

2.1.1 Approval Process

The following outlines the process for individual treatment approvals:

1. An individual application is submitted by the approved consultant to the HSE-Medicines Management Programme (MMP).

2. The HSE-MMP review the application with three possible outcomes:

    a. HSE-MMP make a positive recommendation for treatment

    b. HSE-MMP do not recommend treatment and notifies applicant of same

    c. HSE-MMP require additional information to make a reimbursement recommendation.

Patisiran and vutrisiran

i. HSE-MMP notifies the Office of the Assistant National Director for Acute Operations of their recommendation.
ii. The Office of the Assistant National Director for Acute Operations notifies the prescribing consultant, the Hospital Group CEO and the HSE-MMP of the final decision.

Inotersen

The reimbursement recommendation will be communicated to the approved consultant via email. High Tech prescription for inotersen should be generated on the High Tech Hub (HTH).

2.2 Patient age

Applications for reimbursement approval of patisiran and vutrisiran will only be considered for individuals aged ≥ 18-85 years at time of application. Applications for reimbursement approval of inotersen will only be considered for individuals aged ≥ 18-82 years at time of application.

2.3 Patient diagnosis

For a positive reimbursement recommendation, clinicians will be required to confirm a diagnosis of hATTR amyloidosis with polyneuropathy stage 1 or stage 2 at the time of application. Clinicians must provide evidence of a documented diagnosis based upon the following:

1. Confirmed diagnosis of hATTR amyloidosis with a documented TTR mutation and where relevant a biopsy report,
2. Symptomatic with early-stage neuropathy, defined as:
    a) Polyneuropathy disability (PND) score I to ≤ IIIB, or
    b) hATTR amyloidosis with polyneuropathy stage 1 or 2.

2.3.1 Genetic testing and biopsy

Confirmed genetic diagnosis of hereditary transthyretin amyloidosis is a condition of reimbursement. Tissue biopsy demonstrating amyloid deposits is not mandatory in all cases (e.g. a positive family history).

2.3.2 Disability due to peripheral neuropathy

Clinicians will be required to confirm the stage of polyneuropathy disability in hATTR amyloidosis at the time of application (refer to table 4).

Table 4: Staging of polyneuropathy disability in hATTR amyloidosis

PND score	Score description	*FAP stage	Stage description
0	No impairment	0	No symptoms
I	Sensory disturbances, preserved walking capabilities	1	Unimpaired ambulation, mostly mild sensory and motor neuropathy in the lower limbs
II	Impaired walking capabilities but ability to walk without stick or crutches	2	Assistance with ambulation needed; mostly moderate impairment progression to the lower limbs, upper limbs and trunk
IIIA	Walking only with the help of 1 stick or crutch	2	Assistance with ambulation needed; mostly moderate impairment progression to the lower limbs, upper limbs and trunk
IIIB	Walking only with the help of 2 sticks or crutches	2	Assistance with ambulation needed; mostly moderate impairment progression to the lower limbs, upper limbs and trunk
IV	Confined to a wheelchair or bedridden	3	Wheel-chair bound or bedridden; severe sensory and motor neuropathy of all limbs

FAP: Familial amyloidotic polyneuropathy; PND: Polyneuropathy disability; *hATTR amyloidosis with polyneuropathy was formerly known as FAP

Patient must have hATTR amyloidosis with polyneuropathy stage of 1 or 2 (FAP stage 1 or 2) to be considered for reimbursement approval.

2.4 Patient's clinical history

In line with the exclusion criteria from the APOLLO, HELIOS A and NEURO-TTR trials, the SmPCs and current reimbursement approval for patisiran, vutrisiran and inotersen, reimbursement will not be considered in patients:

- With a platelet count < 100 x 10^9/L prior to treatment (inotersen applications),
- With severe heart failure symptoms (defined as New York Heart Association [NYHA] class III or IV),
- With a prior liver transplant or in patients where a liver transplant is planned,
- With moderate or severe hepatic impairment (severe for inotersen applications),
- With severe renal impairment or end-stage renal disease,
- Using other interfering ribonucleic acid drugs or transthyretin stabilisers used to treat hATTR amyloidosis,
- With other causes of polyneuropathy.

This list is not exhaustive; please refer to the summary of product characteristics for Onpattro® 2mg/ml concentrate for solution for infusion, Amvuttra® 25mg solution for injection and Tegsedi® 284 mg solution for injection, for full prescribing information.

2.4.1 Heart failure

Clinicians are required to confirm if there is cardiac involvement associated with the patient's hATTR amyloidosis. The NYHA classification, N-terminal pro b-type natriuretic peptide/ B-type natriuretic peptide (NT-proBNP/BNP), and a recent echocardiogram (ECHO) are required to be submitted at the time of application.

2.4.2 Liver transplant

Clinicians are required to confirm that the patient has not had a liver transplant at the time of application and that a liver transplant is not planned for the patient.

2.4.3 Hepatic impairment

Clinicians are required to confirm hepatic function by submitting a full liver profile at the time of application.

2.4.4 Renal impairment

Clinicians are required to confirm renal function by submitting a full renal profile at the time of application.

2.4.5 Other causes of polyneuropathy

Clinicians are required to submit supporting evidence to rule out other causes of polyneuropathy at the time of application. Examples of supporting evidence include a full blood count, HbA1c, thyroid stimulating hormone (TSH) levels, vitamin B12 levels, immunoglobulins, serum protein electrophoresis, urine electrophoresis, serum free light chains, immunofixation assay and nerve conduction studies.

2.5 Patient's medical treatment

Clinicians will be required to provide details of the patient's medical treatment at the time of application.

3. Reimbursement criteria – Requirement for outcome data

Follow-up data may be requested by the MMP for audit purposes and provision of same is a condition of ongoing reimbursement. It is the responsibility of the approved consultant to ensure that the patient or their representative/guardian is aware that the provision of follow-up data is a condition of reimbursement, and that audits may occur during which their personal data will be reviewed.

Response to patisiran, vutrisiran or inotersen in adults should be assessed between nine and 12 months. Thereafter, patients should be assessed at least every six months to determine whether they would benefit from continued treatment. Level of disability due to peripheral neuropathy should be documented at the time of follow-up. An up to date ECHO report and diagnostic testing results may be requested at suitable intervals. Follow-up information should be submitted and sent by secure email to the MMP (mmp@hse.ie) when requested outlining:

- Current PND score,
- Any changes to clinical history since initiation,
- Whether patisiran, vutrisiran or inotersen is to be continued or discontinued.

3.1 Discontinuation criteria

Patisiran, vutrisiran and inotersen should be discontinued and reimbursement may no longer be supported if the patient:

- progresses to hATTR amyloidosis stage 3 or PND score IV i.e. the patient is confined to a wheelchair or permanently bedridden and dependent on assistance for basic activities of daily living and/or
- is receiving end-of-life care.

Therefore, following approval of a patient for reimbursement of patisiran, vutrisiran or inotersen under hospital pricing approval or the High Tech Scheme, the approved consultant will be required to submit follow-up information to the MMP, as requested. Follow-up data may be requested by the MMP for audit purposes and provision of same is a condition of ongoing reimbursement approval.

4. Medicines Management

Please refer to the SmPCs for patisirian, vutrisiran and inotersen for full prescribing information including monitoring and patient counselling requirements.

Sites must ensure a local policy is in place for appropriate medicines management, including protocols for the preparation and administration of patisiran and vutrisiran, taking into consideration information outlined in the SmPCs and conditions of the marketing authorisation.

Patisiran: If homecare treatment is implemented this will be paid for by Alnylam (marketing authorisation holder).

Vutrisiran: If homecare treatment is implemented this will be paid for by Alnylam (marketing authorisation holder).
Inotersen: Swedish Orphan Biovitrium Ltd. [(SOBI) (marketing authorisation holder)] have confirmed that a patient support programme will be provided, where requested.

If a patient is recommended for reimbursement by the HSE-MMP, the high tech prescription for inotersen should be generated on the HTH (details outlined separately). High tech prescriptions that are not hub generated for inotersen will not be eligible for reimbursement by the HSE-Primary Care Reimbursement Service (PCRS). Only approved consultants and their teams will have access to generate prescriptions.