Medicines Management Programme

Managed Access Protocol – Patisiran (Onpattro®) for the treatment of hereditary transthyretin-mediated amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy

▼ 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 adverse reactions.

Approved by:	Prof. Michael Barry, Clinical Lead, MMP.
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List of Abbreviations

BNP	B-type natriuretic peptide
ECHO	Echocardiography
FAP	Familial amyloid polyneuropathy
HSE	Health Service Executive
hATTR	Hereditary transthyretin-mediated (amyloidosis)
MAP	Managed Access Protocol
MMP	Medicines Management Programme
NICE	National Institute for Health and Care Excellence
NYHA	New York Heart Association
NT-proBNP	N-terminal pro b-type natriuretic peptide
PND	Polyneuropathy disability
RNAi	Ribonucleic acid interference
siRNA	Small interfering ribonucleic acid
SmPC	Summary of product characteristics
TSH	Thyroid stimulating hormone
TTR	Transthyretin

1. Patisiran

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) 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 the Hospital Arrangement:

- Onpattro® 2mg/ml concentrate for solution for infusion (10mg/5ml vial) ▼[i]

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

1.1 Licensed indication

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

1.2 Reimbursement

Approved prescribers are required to apply for reimbursement approval on an individual patient basis. The *Patisiran Application Form* for the individual recommendation of patisiran should be completed and sent[iii] by secure email to the HSE-Medicines Management Programme (MMP) at mmp@hse.ie.

See Section 2 for further details on Reimbursement criteria – Initiation

1.2.1 Approval Process

The following outlines the process for individual treatment approvals:

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

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

    a. HSE-MMP make a positive recommendation for treatment

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

3. HSE-MMP notifies the Office of the National Director for Acute Operations of their recommendation.

[i] This medicinal product is subject to additional monitoring.
[ii] Please refer to the summary of product characteristics for Onpattro®2mg/ml concentrate for solution for infusion for full prescribing information.
[iii] Post: Prof. Michael Barry, HSE-Medicines Management Programme, Department of Pharmacology and Therapeutics, Trinity Centre for Health Sciences, St James's Hospital, Dublin 8

4. The Office of the National Director for Acute Operations notifies the prescribing consultant, the Hospital Group CEO and the HSE-MMP of the final decision.

Table 1: Licensed dosing of patisiran (Onpattro®) for the treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy

Patient population	Route of administration	Dose
Adults <100kg	IV infusion	300mcg per kg body weight once every three weeks
Adults ≥100kg	IV infusion	30mg once every three weeks

IV: Intravenous, mcg: microgram, kg: kilogram

Please refer to the Summary of Product Characteristics (SmPC) for more information on posology and method of administration

If a patient is recommended and approved for reimbursement of patisiran, reimbursement will be supported for a maximum of three packs of patisiran (a total of 30mg) every three weeks i.e. in line with the licensed dose as per SmPC. *See Section 2 for further details on Reimbursement criteria - Medicines Management*

1.3 Reimbursement price

The cost to the HSE of the presentation(s) of patisiran, available under the Hospital Arrangement as of October 2021, are as follows:

Table 2: Cost* to the HSE of the presentation(s) of patisiran available on the Hospital Arrangement

Strength and (pack size)	Cost to HSE
Onpattro® 2mg/ml concentrate for solution for infusion (1 x 5ml vial)	€8,342.63

ml: millilitre, mg: milligram *Price to wholesaler

Table 3: Annual treatment costs* per patient treated with patisiran according to dosing regimen

Treatment regimen	Cost to HSE per patient per year
Adult requiring 2 vials per treatment	€283,649.42
Adult requiring 3 vials per treatment	€425,474.13

*Price to wholesaler

A commercial in confidence arrangement is in place with the marketing authorisation holder to reduce the net acquisition cost of Onpattro® 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 for the treatment of hATTR amyloidosis with stage 1 or stage 2 polyneuropathy under the Hospital Arrangement.

2.1 Prescribers

The prescribing of patisiran under the Hospital Arrangement will be confined to consultants with experience in the diagnosis and management of hATTR amyloidosis in specialist centre(s) in Ireland, who have agreed to the terms of this managed access protocol (MAP) and have been approved by the HSE.

Applications for reimbursement approval will only be considered from these prescribers.

2.2 Patient age

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

2.3 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-mediated 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

Reimbursement of patisiran will only be supported in patients who fulfil the scoring systems for evaluating hATTR systemic amyloidosis, which includes scores based on disability due to peripheral neuropathy (e.g. the PND score).

Clinicians will be required to confirm the patient's hATTR staging of systemic amyloidosis at the time of application.

Patient must have hATTR amyloidosis with polyneuropathy stage of 1 or 2. *Refer to table 4 for the* hATTR staging of polyneuropathy disability.

Table 4: Staging of hATTR polyneuropathy disability[iv]

PND score	Score description	*FAP stage	Stage description	Patisiran licensed
0	No impairment	0	No symptoms	N
I	Sensory disturbances, preserved walking capabilities	1	Unimpaired ambulation, mostly mild sensory and motor neuropathy in the lower limbs	Y
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	Y
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	Y
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	Y
IV	Confined to a wheelchair or bedridden	3	Wheel-chair bound or bedridden; severe sensory and motor neuropathy of all limbs	N

FAP: Familial amyloid polyneuropathy, PND: Polyneuropathy disability
*hATTR amyloidosis with polyneuropathy was formerly known as FAP

2.4 Patient's clinical history

In line with the exclusion criteria[v] from the APOLLO trial, the SmPC and current reimbursement approval for patisiran, reimbursement will not be considered in patients:

- 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,
- 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.

[iv] National Institute for Health and Care Excellence (NICE) technology appraisal guidance *Patisiran for treating hereditary transthyretin amyloidosis* (HST10)
[v] This list is not exhaustive; please refer to the summary of product characteristics for Onpattro® 2mg/ml concentrate for solution for infusion 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, NT-proBNP/BNP[vi] 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[vii] to rule out other causes of polyneuropathy at the time of application.

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 – Discontinuation

Patisiran 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 under the Hospital Arrangement, the prescribing clinician will be required to submit follow-up information to the MMP,

[vi] BNP: B-type natriuretic peptide, NT-proBNP: N-terminal pro b-type natriuretic peptide.
[vii] For example: 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.

as requested. Follow-up data may be requested by the MMP for audit purposes and provision of same is a condition of ongoing reimbursement.

3.1 Follow-up data

The recommended time frame for assessing a response to patisiran in adults is 9 months. Thereafter, patients should be assessed at least every six months to determine whether they would benefit from continued treatment with patisiran. 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 or stage of hATTR amyloidosis,
- Any changes to clinical history since initiation,
- Whether patisiran is to be continued or discontinued.

4. Reimbursement criteria – Medicines Management

Approved site(s) must ensure a local policy is in place to ensure appropriate medicines management, including protocols for reconstitution and administration of patisiran. If homecare treatment is implemented this will be paid for by Alnylam (marketing authorisation holder).

5. Prescribing of patisiran (Onpattro® 2mg/ml concentrate for solution for infusion)

Please refer to the SmPC for patisiran (Onpattro®) for full prescribing information including monitoring and patient counselling requirements. Only approved prescriber(s) will be able to apply for patisiran reimbursement approval. The following confirmations are required when prescribing patisiran:

- Confirmation that patisiran (Onpattro®) is being prescribed for a MMP approved patient in accordance with the MAP established in line with the terms of reimbursement approval given by the HSE.
- Confirmation that the prescriber will assist the HSE/MMP in their conduct of audits* through provision of information as requested, to provide assurance that the product is being prescribed in line with HSE reimbursement approval and the MAP.
- Confirmation that the patient is aware that the application for reimbursement approval is being made on their behalf and that audits may occur during which their personal data will be reviewed.

* Follow-up data may be requested by the HSE/MMP for audit purposes and provision of same is a condition of ongoing reimbursement.