Medicines Management Programme

Managed Access Protocol – Inotersen (Tegsedi®▼) 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

ASO	Antisense oligonucleotide
BNP	B-type natriuretic peptide
ECHO	Echocardiography
FAP	Familial amyloid polyneuropathy
HSE	Health Service Executive
IMC	Irish Medical Council
hATTR	Hereditary transthyretin-mediated (amyloidosis)
HTH	High Tech Hub
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
SC	Subcutaneous
SmPC	Summary of product characteristics
SOBI	Swedish Orphan Biovitrum Ltd.
TSH	Thyroid stimulating hormone
TTR	Transthyretin

1. Inotersen

Inotersen (Tegsedi®) is a 2'-*O*-2-methoxyethyl (2'-MOE) phosphorothioate antisense oligonucleotide (ASO) inhibitor of human transthyretin (TTR) production. The selective binding of inotersen to the TTR messenger RNA (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 pre-filled syringe (PFS) ▼[i]

1.1 Licensed indication

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

1.2 Reimbursement

Approved prescribers are required to apply for reimbursement approval on an individual patient basis. The *Inotersen Application Form* for the individual recommendation of inotersen should be completed and sent[iii] by secure email to the Health Service Executive (HSE)-Medicines Management Programme (MMP) at mmp@hse.ie. *See Section 2 for further details on Reimbursement criteria – Initiation*

If a patient is recommended and approved for reimbursement by the MMP, the High Tech prescription for inotersen should be generated on the High Tech Hub (HTH). High tech prescriptions which are not hub generated will not be eligible for reimbursement by the HSE-Primary Care Reimbursement Service (PCRS).

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

Patient population	Route of administration	Dose
Adult patients	SC	284 mg once every week (on the same day each week)

mg: milligram; SC: Subcutaneous

Please refer to the Summary of Product Characteristics (SmPC) for more information on posology and method of administration including *dose adjustment in case of reduction in platelet count*

[i] This medicinal product is subject to additional monitoring.
[ii] Please refer to the summary of product characteristics for Tegsedi® 284 mg solution for injection in pre-filled syringe 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

If a patient is recommended and approved for reimbursement of inotersen, reimbursement will be supported for a maximum of one pack (containing four PFSs) every four weeks i.e. in line with the licensed dose as per SmPC. *See Section 2 for further details on Reimbursement criteria - Initiation*

1.3 Reimbursement price

The reimbursement price of Inotersen (Tegsedi®) available on the High Tech Arrangement as of 1st October 2022, is as follows:

Table 2: Reimbursement price of the presentation of inotersen available on the High Tech Arrangement

	Reimbursement	
Strength and (pack size)	**Code**	**Price**
Tegsedi® 284 mg solution for injection (4 x 1.5 ml PFS)	89227	€24,154.75

mg: milligram; ml: millilitre; PFS: pre-filled syringe * price is correct as of 1st October 2022

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

2.1 Prescribers

The prescribing of inotersen under the High Tech 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 ≥ 18-82 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 inotersen 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 3 for the* hATTR staging of polyneuropathy disability.

Table 3: Staging of hATTR polyneuropathy disability[iv]

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

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 NEURO-TTR trial, the SmPC and current reimbursement approval for inotersen, reimbursement will not be considered in patients:

- With a platelet count < 100 x 10^9/L prior to treatment,
- 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 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] For the purpose of this Managed Access Protocol (MAP), definitions for staging of hATTR polyneuropathy disability are based on the National Institute for Health and Care Excellence (NICE) guidance (HST10) and also reflects the definition used in the HSE-Medicines Management Programme (MMP): MAP – Patisiran (Onpattro®) for the treatment of hereditary transthyretin-mediated amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy. Available at: https://www.hse.ie/eng/about/who/cspd/ncps/medicines-management/managed-access-protocols/patisiran-onpattro/patisiran-onpattro-map.pdf

[v] This list is not exhaustive; please refer to the summary of product characteristics for Tegsedi® 284 mg solution for injection in pre-filled syringe for full prescribing information.

2.4.1 Platelet count

Clinicians are required to confirm the patient's platelet count at the time of application. A full blood count is required to be submitted at the time of application.

2.4.2 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.

2.4.3 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.

2.4.4 Hepatic impairment

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

2.4.5 Renal impairment

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

2.4.6 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.

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

[vii] For example: 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 will be required.

3. Reimbursement criteria – Discontinuation

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 inotersen under the High Tech Arrangement, the prescribing clinician 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.

3.1 Follow-up data

The recommended time frame for assessing a response to inotersen 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 inotersen. 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 inotersen is to be continued or discontinued.

4. Reimbursement criteria – Medicines Management

Swedish Orphan Biovitrum Ltd. [(SOBI) (marketing authorisation holder)] have identified that a patient support programme will be provided, where requested.