patisiran 2mg/mL concentrate for solution for infusion (Onpattro®)
Alnylam Pharmaceuticals

10 May 2019

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

**ADVICE**: following a full submission assessed under the ultra-orphan medicine process patisiran (Onpattro®) is accepted for use within NHSScotland.

**Indication under review**: the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy.

In a phase III study of adults with hATTR amyloidosis and polyneuropathy, patisiran was associated with significant improvements compared with placebo, measured by the change in modified neuropathy impairment score +7 (mNIS+7) from baseline to 18 months.

This SMC advice takes account of the benefit of a Patient Access Schemes (PAS) that improves the cost-effectiveness of patisiran. This advice is contingent upon the continuing availability of the PAS in NHSScotland or a list price that is equivalent or lower.

This advice takes account of views from a Patient and Clinician Engagement (PACE) meeting.

Chairman
Scottish Medicines Consortium
**Indication**
The treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy. ¹

**Dosing Information**
The recommended dose of patisiran is 300 micrograms/kg body weight administered via intravenous infusion once every 3 weeks. For patients weighing ≥100 kg, the maximum recommended dose is 30mg. It is recommended that patients receiving patisiran are given vitamin A supplementation at a daily dose of approximately 2,500 international units.

Patisiran must be diluted prior to infusion. To reduce the risk of infusion-related reactions premedication should be administered. Please refer to the summary of product characteristics for further information.

Therapy should be initiated under the supervision of a physician knowledgeable in the management of amyloidosis. ¹

**Product availability date**
June 2019.

Patisiran has been designated an orphan medicine for the treatment of ATTR amyloidosis by the European Medicines Agency (EMA).

Patisiran received a positive scientific opinion for the treatment of adults with hATTR amyloidosis under the Early Access to Medicines Scheme with the Medicines and Healthcare Products Regulatory Agency on 3 August 2018.

Patisiran meets SMC ultra-orphan criteria.

**Background**
Patisiran is a double-stranded small interfering ribonucleic acid (siRNA). It is formulated as lipid nanoparticles to deliver siRNA to hepatocytes, the primary source of transthyretin (TTR) protein. It specifically targets a sequence within TTR mRNA, both mutant and wild-type, causing the degradation of TTR mRNA in the liver, thereby reducing serum TTR protein. ¹ ²
Patisiran for use in this indication has been considered by SMC using its decision-making framework for the assessment of ultra-orphan medicines.

Nature of condition

hATTR amyloidosis is a rare, life-threatening, autosomal dominant disease caused by mutations in the TTR gene. This leads to production of abnormal TTR protein in the liver which accumulates as deposits in the tissues of the body (amyloidosis). Since amyloid deposits can affect tissues throughout the body, patients can experience a range of symptoms affecting the nervous system, heart, gastrointestinal tract, eyes and central nervous system. Diagnosis typically occurs in the seventh decade of life when the disease manifests with polyneuropathy and cardiomyopathy. It is a rapidly progressive, debilitating disease with high mortality, and predominantly affects males (approximately 3:1 male to female ratio).

Treatment options for hATTR amyloidosis are limited and largely restricted to supportive measures. Orthotopic liver transplant is an option for a minority of patients. Tafamidis is a TTR tetramer stabiliser that is not recommended for use by SMC due to non-submission. Diflunisal, an unlicensed oral non-steroidal anti-inflammatory has been shown to reduce neuropathy, however treatment should be carefully considered in patients with cardiovascular disease. The antisense oligonucleotide inotersen has recently received a marketing authorisation from the European Medicines Agency (EMA) and is currently undergoing assessment by SMC. Estimates of survival with currently available treatment vary depending on the genotype and phenotype and whether or not there is cardiac amyloidosis, but the patisiran Orphan Maintenance Assessment Report notes a life expectancy of 3 to 15 years from symptom onset.\textsuperscript{2,5} Patisiran is the first medicine of the siRNA class to be licensed in Europe. Clinical experts consulted by SMC considered that patisiran fills an unmet need in this therapeutic area, as there are currently no disease modifying treatments routinely available. It is a designated EMA orphan medicine and meets SMC ultra-orphan criteria.

A patient and clinician engagement (PACE) meeting was held to consider the added value of patisiran in the context of treatments currently available in NHSScotland. At the PACE meeting, attention was drawn to the devastating and relentlessly progressive nature of the disease. Patients usually experience multiple symptoms, including sensory, motor and autonomic deficits and, for some patients, cardiac involvement. The heavy symptom burden affects all areas of a patients’ life and consequently families and carers. It can eventually lead to a complete loss of independence and dignity.
Summary of evidence on comparative efficacy

The efficacy of patisiran in patients with hATTR amyloidosis with polyneuropathy was investigated over 18 months in the multicentre, randomised, double-blind, placebo-controlled phase III APOLLO study.\(^2,3\) Eligible patients were adults aged 18 to 85 years, diagnosed with hATTR amyloidosis and documented TTR mutation, with a life expectancy of at least two years. Patients were required to have a neuropathy impairment score (NIS) of 5 to 130 (range 0 to 244, with higher scores indicating more impairment), a polyneuropathy disability (PND) score of IIIb or lower (with higher scores indicating more impaired walking ability) and Karnofsky performance status of at least 60%.

Patients were randomised in a 2:1 ratio to patisiran 300 micrograms/kg or placebo administered by intravenous (IV) infusion over 80 minutes once every three weeks. Randomisation was stratified according to NIS, age at onset of disease and pathogenic variant, and previous use of a TTR stabiliser. All patients received premedication, at least one hour prior to study medication infusion, with IV corticosteroid, antihistamine (H1 and H2 antagonists) and oral paracetamol to reduce the potential for infusion-related reactions.\(^2,3\)

The primary outcome was the change from baseline to 18 months in modified neuropathy impairment score +7 (mNIS+7). This is a composite score that measures a range of motor, sensory, and autonomic neurologic impairments experienced by patients with hATTR-polyneuropathy.\(^2\) The mNIS+7 ranges from 0 to 304, with higher scores indicating more impairment.\(^3\) The primary outcome was compared between patisiran and placebo in the modified intent to treat (mITT) population, defined as all randomised patients who received at least one dose of the study treatment. At 18 months, the mean mNIS+7 score decreased from baseline in the patisiran group (indicating an improvement in the underlying neuropathy) and increased in the placebo group (indicating a worsening), with a significant between group difference favouring patisiran, see table 1.

### Table 1. Primary outcome in the APOLLO study\(^2,3\)

<table>
<thead>
<tr>
<th></th>
<th>Patisiran</th>
<th>Placebo</th>
<th>LSM difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>mNIS+7 (LSM)</td>
<td>n=148</td>
<td>n=77</td>
<td></td>
</tr>
<tr>
<td>Baseline (mean), points</td>
<td>80.9</td>
<td>74.6</td>
<td></td>
</tr>
<tr>
<td>LSM change from baseline, points</td>
<td>-6.0</td>
<td>+28.0</td>
<td>-34.0 (95% CI: -39.9 to -28.1; p&lt;0.001)</td>
</tr>
</tbody>
</table>

LSM: least squares mean; mNIS+7: modified neuropathy impairment score +7, CI: confidence interval
The secondary outcomes assessed the difference between patisiran and placebo in the change from baseline in the following measurements at 18 months and were tested in a hierarchical manner:

- Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN) questionnaire (range -4 to 136 with higher scores indicating worse quality of life)
- Neurological impairment score-weakness (NIS-W) (range 0 to 192 with higher scores indicating more impairment)
- Rasch-built Overall Disability Scale (R-ODS) (range 0 to 48 with lower scores indicating more disability)
- Timed 10-metre walk test (10-MWT; gait speed measured in metres per second)
- Modified body mass index (mBMI) which includes albumin level as well as weight and height (lower values indicate worse nutritional status)
- Autonomic symptoms questionnaire (Composite Autonomic Symptom Score [COMPASS 31], range 0 to 100 with higher scores indicating more autonomic symptoms).

These end points all significantly favoured patisiran over placebo, see table 2.

Table 2 Secondary efficacy endpoints at 18 months (mITT population)³

<table>
<thead>
<tr>
<th></th>
<th>Patisiran</th>
<th>Placebo</th>
<th>LSM difference*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norfolk QoL-DN</td>
<td>(n=136)</td>
<td>(n=48)</td>
<td></td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>59.6</td>
<td>55.5</td>
<td></td>
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<tr>
<td>LSM change from baseline</td>
<td>-6.7</td>
<td>14.4</td>
<td>-21.1</td>
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<tr>
<td>NIS-W</td>
<td>(n=137)</td>
<td>(n=51)</td>
<td></td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>32.7</td>
<td>29.0</td>
<td></td>
</tr>
<tr>
<td>LSM change from baseline</td>
<td>0.1</td>
<td>17.9</td>
<td>-17.9</td>
</tr>
<tr>
<td>R-ODS</td>
<td>(n=138)</td>
<td>(n=54)</td>
<td></td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>29.7</td>
<td>29.8</td>
<td></td>
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<tr>
<td>LSM change from baseline</td>
<td>0</td>
<td>-8.9</td>
<td>9.0</td>
</tr>
<tr>
<td>10-MWT</td>
<td>(n=138)</td>
<td>(n=55)</td>
<td></td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>0.80</td>
<td>0.79</td>
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</tr>
<tr>
<td>LSM change from baseline</td>
<td>0.08</td>
<td>-0.24</td>
<td>0.31</td>
</tr>
<tr>
<td>mBMI</td>
<td>(n=133)</td>
<td>(n=52)</td>
<td></td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>969.7</td>
<td>989.9</td>
<td></td>
</tr>
<tr>
<td>LSM change from baseline</td>
<td>-3.7</td>
<td>-119.4</td>
<td>115.7</td>
</tr>
<tr>
<td>COMPASS 31</td>
<td>(n=136)</td>
<td>(n=53)</td>
<td></td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>30.6</td>
<td>30.3</td>
<td></td>
</tr>
<tr>
<td>LSM change from baseline</td>
<td>-5.3</td>
<td>2.2</td>
<td>-7.5</td>
</tr>
</tbody>
</table>

LSM: least squares mean, Norfolk QOL-DN: Norfolk Quality of Life-Diabetic Neuropathy; NIS-W: Neurological impairment-weakness; R-ODS: Rasch-built Overall Disability Scale; 10-MWT: timed 10-
meter walk test; mBMI: modified body mass index; COMPASS 31: Composite Autonomic Symptom Score; *p<0.001 for all comparisons.

Patisiran reduced serum transthyretin levels by a median of 81% (range -38 to 95) and this reduction was maintained throughout the study period. Overall, subgroup analyses showed a consistent difference in change from baseline in mNIS+7 in favour of patisiran compared with placebo across all subgroups, including in a pre-defined cardiac subpopulation. In addition, the treatment effect was consistent across the components of the mNIS+7.

Analysis of neuropathy stage was an exploratory endpoint. In the patisiran group, the polyneuropathy disability (PND) score at 18 months was stable or improved in 73% of patients (8.1% improved and 65% stable) when compared with baseline scores. While 30% of patients in the placebo group stabilised, none showed an improvement in the PND score at 18 months.

Patients completing the 18-month efficacy assessments were eligible to participate in the ongoing global open-label extension study (NCT02510261) in which patients receive patisiran 300 micrograms/kg IV infusion every 3 weeks for up to 5 years. Interim mNIS+7 data analysis suggests stabilisation of neuropathy in all patients receiving patisiran at 52 weeks in the open-label extension, including those who had previously received placebo in APOLLO.

Summary of evidence on comparative safety

In APOLLO, the mean duration of study treatment was 17.7 months and 15 months in the patisiran and placebo groups, respectively. The proportion of patients in each treatment group who experienced an adverse event was 97%, most of which were mild or moderate in severity. However, the proportion of patients who experienced an adverse event that was considered to be related to treatment was higher in the patisiran group (49%) compared with the placebo group (39%). A similar proportion of patients in each treatment group experienced a serious adverse event (36% and 40% in the patisiran and placebo groups, respectively). Adverse events leading to discontinuation of study treatment, or to withdrawal from the study, occurred more frequently in the placebo group than in the patisiran group: treatment was discontinued in 14% of placebo-treated patients and 4.7% of patisiran-treated patients.

The most common adverse events were diarrhoea (37% and 38% of patients in the patisiran and placebo groups, respectively), peripheral oedema (30% and 22%), infusion-related reaction (19% and 8.9%), falls (17% and 29%), constipation (15% and 17%), nausea (15% and 21%) and urinary tract infection (13% and 18%).

To reduce the risk of infusion related reactions, patients should receive premedications on the day of patisiran infusion. In patients who experience infusion related reactions a slower infusion rate or additional or higher doses of one or more of the premedications should be considered.
Patisiran treatment can lead to a decrease in serum vitamin A levels. The SPC recommends that oral supplementation should be prescribed and referral for ophthalmological assessments should be made if there are symptoms suggestive of vitamin A deficiency.¹

**Summary of clinical effectiveness issues**

In the phase III study of patients with hATTR amyloidosis and polyneuropathy, symptoms of neuropathy improved in the patisiran group and worsened in the placebo group, measured by the primary outcome mNIS+7. The EMA considered that the minimum clinically important difference in mNIS+7 was 2 points. The change from baseline of 6-points in the patisiran group exceeds this. Additional training and multiple assessments were carried out to standardise the efficacy assessment and reduce variability. The results were statistically significant and clinically relevant and were supported by all secondary outcomes which included patient reported outcomes. There was consistency of treatment effect across components of primary outcome and across the different subgroups.² ⁵

The long-term effectiveness of patisiran is currently unknown. The APOLLO study was primarily designed to show efficacy on polyneuropathy. Exploratory surrogate endpoints were analysed in a cardiac subpopulation to determine the effect of patisiran on cardiac manifestations. While results indicate that patisiran treatment has a positive impact on cardiac parameters⁸, the EMA noted that a clinically relevant benefit for cardiac symptoms is currently uncertain.² The APOLLO study excluded patients with NYHA class III or IV so the treatment effect in patients with significant symptoms of heart failure is unknown. In addition, the exclusion of patients with type I diabetes and type II diabetes for ≥5 years limits generalisability to these patients. The economic model submitted by the company extrapolates clinical benefit shown in the APOLLO study and predicts a mean survival gain of 4.59 life years.

Clinical experts consulted by SMC considered that patisiran is a major therapeutic advancement due to the clinically significant improvement in symptoms in the clinical studies, they noted that patisiran improved quality of life and reduced disability compared with the control.

At the PACE meeting, it was noted that patisiran offers compelling benefits in the management of this disease, being the first medication to tackle the underlying defect in hATTR amyloidosis through suppression of TTR protein production by the liver. PACE clinicians described the results of the clinical studies as remarkable and unprecedented for this disease area. Patisiran has the potential to halt or slow progression of the disease and in some cases improve symptoms. Improvements in symptom control, in particular diarrhoea, would have a massive impact on patients’ and quality of life and on carers. Improvements in postural hypotension and neuropathy could potentially reduce fracture risk.
A PACE meeting with patient group representatives and clinical specialists was held to consider the added value of patisiran as an ultra-orphan in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- hATTR amyloidosis is a rare, devastating progressive hereditary disease. Patients usually experience multiple symptoms, including sensory, motor and autonomic deficits and, for some patients, cardiac involvement. The heavy symptom burden affects all areas of a patients’ life and consequently families and carers. It can eventually lead to a complete loss of independence and dignity.
- There is significant unmet need: no treatments are available for use that target the underlying defect in hATTR amyloidosis.
- Current approaches to manage the distressing symptoms have limited effectiveness and may often be associated with side effects.
- Patisiran offers a significant advance in the management of this disease being the first medication to tackle the underlying defect in hATTR amyloidosis. PACE clinicians described the results of the key study as remarkable.
- Patisiran has the potential to halt or slow progression of the disease and in some cases improve symptoms. With the expectation of continued clinical improvement throughout the duration of TTR lowering. Improvements in symptom control, in particular diarrhoea, would have a massive impact on patients’ and carers’ quality of life. Improvements in postural hypotension and neuropathy could potentially reduce fracture risk.
- Patisiran is generally well tolerated and administration by home care or in a day ward is likely to be suitable.

Additional Patient and Carer Involvement

We received a patient group submission from the Amyloidosis Research Consortium UK (ARC UK), which is a registered charity. ARC UK has received 80% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from ARC UK participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.
The company submitted a cost-utility analysis comparing patisiran plus best supportive care (BSC) to BSC alone for the treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy. BSC was assumed to consist of pharmacological and/or surgical treatment to alleviate polyneuropathy and cardiomyopathy symptoms. A lifetime (40-year) Markov model was provided consisting of 13 health states which were defined primarily according to PND score, a measure of neuropathy progression. Patients in PND state 0 were asymptomatic whilst those in PND IV were confined to a wheelchair or bedridden. The model was also stratified according to cardiomyopathy severity, based on the N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) biomarker. Patients with NT-proBNP above 3000pg/mL were assumed to have a higher risk of mortality.

The starting distribution of patients across health states was derived from the pivotal study. At each 6 monthly cycle patients move across PND and NT-proBNP states based on transition probabilities from the APOLLO study. Based on these data, a higher proportion of patients in the patisiran arm remained in the lower PND states than patients receiving BSC. Long term transition probabilities for the patisiran arm of the model were assumed to remain the same over time i.e. transition probabilities observed within the 18 month study were extrapolated over the duration of the model for both arms. For the BSC, long term transition probabilities were based on the the placebo arm of the APOLLO study. Time on treatment for patisiran was estimated by fitting a log-normal curve to patient level data from the pivotal study. Risk of death by PND and NT-proBNP within the model were based on published literature. Utility values were based on quality of life data collected from the pivotal study. EQ-5D-5L data were mapped to EQ-5D-3L values using a published equation. In addition, the model also includes a differential utility effect. For patisiran, patients were assumed to experience a monthly increase in utility whilst those on standard of care were assumed to experience a monthly decrease in utility. The company justified this differential based on observed data from the pivotal study. Sensitivity analyses were provided to show the inclusion of carer disutilities.

Medicine acquisition, administration and premedication costs were included for patisiran. Premedication was assumed to be IV dexamethasone, H₁ and H₂ blockers and oral paracetamol (given 60 minutes prior to each infusion). The dose for patisiran used in the economic analysis was weight based. Based on data from the pivotal study, the analysis assumes 2.38 vials per dose, given every 3 weeks. A relative dose intensity of 97% was also incorporated. Health state costs for each PND state were estimated based on a Delphi panel. The model captures end of life costs and the cost of treating adverse events.
Miscellaneous costs such as electric wheelchairs and structural adjustments to patients’ homes have also been included.

A Patient Access Scheme (PAS) was proposed by the submitting company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland.

SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. The submitting company has also requested that the list price results are not presented and as such no cost-effectiveness results can be presented.

There were some weaknesses with the analysis which were as follows:

- There is some uncertainty surrounding the modelled outcomes (PND and NT-proBNP), which were used to capture polyneuropathy and cardiomyopathy progression. In terms of polyneuropathy, PND captures mobility concerns however it may not capture other important elements of the condition such as autonomic symptoms. Overall, the modelled outcomes appear broadly reasonable, but may not capture all the aspects of the condition. The submitting company provided some additional analysis to include disutility impacts associated with the GI effects of autonomic dysfunction on BSC-treated patients.

- In the base case analysis the company assumes that long term transition probabilities for patisiran and BSC are likely to be reflective of those from the 18 month pivotal study. However, due to the lack of long term data supporting this assumption, this may not be appropriate. The company was asked to provide an additional scenario analysis which incorporates a waning of patisiran treatment effect. The company indicated that it was challenging to adjust transition probabilities within the model to reflect a reduction in patisiran efficacy, therefore a 0.5% reduction in efficacy was applied to the patisiran treatment arm every 6 months. Results were not overly sensitive to this which may reflect that patients were assumed to have a complete cessation of efficacy and discontinue treatment in this scenario (i.e. would reduce both costs and outcomes).

- There were some concerns that due to the inclusion of monthly differential values, it appeared plausible that patients on BSC in a low PND state (earlier disease stage) could have a poorer quality of life than a patient receiving patisiran in a higher PND state (later disease stage). This suggests the approach may lack a degree of validity. Some sensitivity analysis has been provided by the company which individually varies the monthly utility change in each arm. However an analysis which removes monthly utility differentials for both treatment arms was not provided as the company argued that data from a post-hoc analysis of EQ-5D data from APOLLO supported a change in utility value over time within a PND state and between treatment arms.
• The company noted that there were some patients from APOLLO with missing data for PND score and/or NT-NT. These missing data were omitted from the analysis when estimating transition probabilities for patisiran and BSC arms, which may introduce additional uncertainty. To address uncertainty, the company provided a conservative scenario analysis which assumes that for the missing data, patients receiving patisiran progressed to next worst health state whilst BSC patients assumed to improve. This analysis was useful and results were reasonably sensitive to this assumption.

• As robust mortality data linking polyneuropathy and cardiomyopathy to survival were not available from the pivotal study, the company therefore used published literature to estimate mortality hazard ratios within the model. Due to the limitations surrounding the published literature, the company provided some sensitivity analysis which removed mortality associated with polyneuropathy and cardiomyopathy. The base case ICER was not overly sensitive to these scenarios; the life year gain/QALY gain decreased considerably but so too did the incremental costs as account of removing life years that would be associated with treatment and care costs in the model.

• Health state costs were estimated based on input from a Delphi panel. The per cycle health state cost for PND IV was somewhat high relative to the other health state costs within the model. As a higher proportion of patients in the BSC arm transition into this health state there is potential that costs in the BSC arm could be overestimated. To address uncertainty around the cost of this health state, the company provided sensitivity analysis which uses a lower cost for PND IV. The ICER was somewhat sensitive to this change.

*Other data were also assessed but remain confidential.*

Impact beyond direct health benefits and on specialist services

At the PACE meeting, attention was drawn to the high psychological and emotional burden of hATTR amyloidosis on patients and their families. It can also have a significant negative financial impact on families if they have to give up work to provide full-time care. Patisiran has the potential to have a major effect on the lives of family members, both psychologically in terms of their own future health should they develop hATTR amyloidosis, and also by reducing the physical and emotional care needs of the patient.

Management of hATTR amyloidosis is highly specialised and is undertaken at The National Amyloidosis Centre in London. Treatment is initiated there and patients are followed up every six months. The submitting company anticipates that patisiran treatment will be initiated at the national centre but that continuation of care will be through shared care arrangements with local clinicians in NHSScotland.
PACE participants highlighted that patisiran, administered as an intravenous infusion with premedication, is generally well tolerated with mild infusion reactions reported. Monitoring should be minimal however staff with experience to understand the difference between intercurrent illnesses and adverse effects will be required. A pathway of care will need to be developed in Scotland to meet patients’ needs. Home care or administration in a day unit would likely be suitable. Patient group participants advised that patients expressed a preference for the treatment to be delivered closer to home where possible.

**Costs to NHS and Personal Social Services**

The company assumed that the number of patients eligible for treatment was 18 in all years to which confidential estimates of treatment uptake were applied.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

The submitting company did not estimate any costs outside the NHS.

*Other data were also assessed but remain confidential.*

**Conclusion**

The Committee also considered the benefits of patisiran in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that a number of the criteria were satisfied: a substantial improvement in quality of life; and the absence of other treatments of proven benefit. In addition, as patisiran is an ultra orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted patisiran for use in NHSScotland.

**Additional information: guidelines and protocols**

No national guidelines relating to hATTR amyloidosis were identified.
There are no medicines in routine use. The antisense oligonucleotide inotersen has recently received a marketing authorisation from the EMA and is currently undergoing assessment by SMC.

**Cost of relevant comparators**

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<thead>
<tr>
<th>Medicine</th>
<th>Dose Regimen</th>
<th>Cost per year (£)</th>
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<tbody>
<tr>
<td>Patisiran</td>
<td>300 micrograms/kg body weight IV infusion every 3 weeks.</td>
<td>£261,000</td>
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</tbody>
</table>

Costs from company submission for patisiran. Costs calculated using a body weight of 70kg and the full cost of vials assuming wastage. Costs do not take any patient access schemes into consideration.
References


This assessment is based on data submitted by the applicant company up to and including 13 April 2019.

*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to
receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

**Advice context:**

*No part of this advice may be used without the whole of the advice being quoted in full.*

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.