

# Patisiran for treating hereditary transthyretin amyloidosis

Highly specialised technologies guidance

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## Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the [Yellow Card Scheme](#).

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should [assess and reduce the environmental impact of implementing NICE recommendations](#) wherever possible.

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# 1 Recommendations

- 1.1 Patisiran is recommended, within its marketing authorisation, as an option for treating hereditary transthyretin amyloidosis in adults with stage 1 and stage 2 polyneuropathy. It is recommended only if the company provides patisiran according to the [commercial arrangement](#).

## Why the committee made these recommendations

Hereditary transthyretin amyloidosis is a rare condition that severely affects the health and quality of life of people with the condition, as well as the quality of life of their families and carers. At the time of the evaluation, there were no disease-modifying treatments in widespread use.

Clinical trial evidence shows that patisiran reduces disability and improves quality of life, by enabling patients to return to work, carry out daily activities, participate in a more active family and social life, and maintain their independence and dignity. There is also evidence suggesting that patisiran may provide long-term benefits by stopping the progression of amyloidosis and potentially reversing it.

Some assumptions in the economic modelling are uncertain, particularly around the utility values and the modelling of mortality. Also, the range of cost-effectiveness estimates presented is somewhat higher than what NICE usually considers acceptable for highly specialised technologies. However, taking additional factors into account, such as the uncaptured health-related benefits of stopping and potentially reversing the condition, the rarity and severity of the condition, the potential lifetime benefit for people with the condition and the innovative nature of the treatment, patisiran is recommended for use in the NHS.

## 2 The condition

- 2.1 Hereditary transthyretin (hATTR) amyloidosis is an ultra-rare condition caused by inherited mutations in the transthyretin (TTR) gene. This causes the liver to produce abnormal TTR protein, which accumulates as deposits in body tissues (amyloidosis). These deposits can disrupt the structure and damage the function of affected tissues.
- 2.2 Because hATTR amyloidosis can affect tissues throughout the body, people may have a range of symptoms relating to 1 or more systems. These can include the autonomic nervous system, peripheral nerves, heart, gastrointestinal system, eyes and central nervous system. The effects and complications of the condition can lead to death within 3 to 15 years of symptoms developing. At the time of the evidence submission, there were thought to be around 150 people with hATTR amyloidosis in the UK.
- 2.3 Scoring systems for evaluating hATTR amyloidosis include scores based on disability due to peripheral neuropathy, for example, the polyneuropathy disability (PND) score and the familial amyloidotic polyneuropathy (FAP) stage (Coutinho et al. 1980). A description of each and the relationship between PND scores and FAP stages is reported in [table 1](#).

**Table 1 Description and relationship between PND scores and FAP stages**

Polyneuropathy disability score	Score description	Familial amyloidotic polyneuropathy stage	Stage description
0	No impairment	0	No symptoms
I	Sensory disturbances, preserved walking capability	1	Unimpaired ambulation; mostly mild sensory and motor neuropathy in the lower limbs

Polyneuropathy disability score	Score description	Familial amyloidotic polyneuropathy stage	Stage description
<b>II</b>	Impaired walking capability but ability to walk without a stick or crutches	<b>2</b>	Assistance with ambulation needed; mostly moderate impairment progression to the lower limbs, upper limbs and trunk
<b>IIIA</b>	Walking only with the help of 1 stick or crutch	<b>2</b>	Assistance with ambulation needed; mostly moderate impairment progression to the lower limbs, upper limbs and trunk
<b>IIIB</b>	Walking with the help of 2 sticks or crutches	<b>2</b>	Assistance with ambulation needed; mostly moderate impairment progression to the lower limbs, upper limbs and trunk
<b>IV</b>	Confined to a wheelchair or bedridden	<b>3</b>	Wheelchair-bound or bedridden; severe sensory and motor neuropathy of all limbs

2.4 While some people with hATTR may mainly have either polyneuropathy or cardiomyopathy symptoms, most patients seen in the NHS will have both over the course of the condition. In the UK, the most common genetic mutations associated with combined polyneuropathy and cardiac involvement are Val122Ile (39%), Thr60Ala (25%) and Val30Met (17%). The Val30Met mutation is associated with higher survival rates. Val122Ile is primarily associated with cardiomyopathy.

2.5 At the time of the evaluation, treatment options for people with hATTR amyloidosis were limited. They mainly focused on symptom relief and supportive care (including pain management, and nutritional and mobility support), and lessening the effects of the condition on other organs (for example, pacemakers, arrhythmia management). During the evaluation of patisiran, [NICE published its](#)

highly specialised technology guidance on inotersen, recommending it, within its marketing authorisation, as an option for treating stage 1 and stage 2 polyneuropathy in adults with hATTR amyloidosis. Other pharmacological treatments may be used, including diflunisal, which is sometimes used outside of its marketing authorisation to treat hATTR amyloidosis. It is contraindicated in people with cardiac impairment and those taking anticoagulants.

- 2.6 Liver transplant, which prevents the formation of additional amyloid deposits, might be an option for some people. However, a transplant can only be done early in the course of the condition, and outcomes are poor in people with cardiac involvement, so it is rarely done in England.
- 2.7 The National Amyloidosis Centre in London provides the only highly specialised service for people with amyloidosis and related disorders in the UK. People with hATTR amyloidosis are assessed (for overall clinical status, neuropathy progression and cardiac involvement) and followed up every 6 months at the Centre, and treatment is started there. The company proposes that people would start treatment with patisiran at the Centre and then, if appropriate, choose whether to continue to have treatment there or at home. At the second meeting, the company explained that some people already have patisiran at home after having 3 infusions in the Centre, and that this is expected to become the routine place for patisiran administration in clinical practice.

### 3 The technology

- 3.1 Patisiran (Onpattro, Alnylam) is a ribonucleic acid interference agent that suppresses transthyretin (TTR) production by the liver (including abnormal TTR). It is administered once every 3 weeks by intravenous infusion at a dose of 0.3 mg/kg. It has a marketing authorisation in the UK for treating 'hereditary transthyretin-mediated amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy'.
- 3.2 The most common adverse reactions listed in the summary of product characteristics for patisiran include peripheral oedema, infusion-related reactions, infections, vertigo, dyspnoea, dyspepsia, erythema, arthralgia and muscle spasms. For full details of adverse reactions and contraindications, see the summary of product characteristics.
- 3.3 The price of patisiran is £7,676.45 per 10-mg vial (excluding VAT; company submission). The company has a [commercial arrangement](#). This makes patisiran available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.



## 4 Consideration of the evidence

The evaluation committee (see [section 6](#)) considered evidence submitted by Alnylam, the views of people with the condition, those who represent them and clinical experts, NHS England and a review by the evidence review group (ERG). See the [committee papers](#) for full details of the evidence. In forming the recommendations, the committee took into account the full range of factors that might affect its decision, including in particular the nature of the condition, the clinical effectiveness, value for money and the impact beyond direct health benefits.

### Nature of the condition

#### Burden of disease

- 4.1 The patient and clinical experts explained the all-consuming nature of hereditary transthyretin (hATTR) amyloidosis. They highlighted that the condition affects all aspects of the lives of patients, and their families and carers. It is a multi-system condition, which has a considerable effect on patients' independence, dignity, and their ability to work, take part in family and social life, and carry out daily activities. They also highlighted that patients need a high level of care as the condition progresses. The clinical experts explained that the clinical signs of hATTR amyloidosis are heterogeneous, and can be associated with a very wide range of impairments.
- 4.2 The neurological deficit associated with hATTR amyloidosis progresses to the legs and the upper limbs. A survey by Amyloidosis Research Consortium UK collected information on 101 patients and 51 carers with experience of the condition. It showed that 86% of patients have numbness, tingling or pain in the lower part of their body, and 74% have muscle weakness and difficulty walking or climbing stairs. Autonomic symptoms typically include dizziness or fainting, vomiting, severe diarrhoea or constipation or both, and neurogenic bladder (lack of bladder control); 38% of patients in the survey reported having faecal or urinary incontinence that considerably impairs their quality of life. Symptoms may severely affect patients' professional and social life. The patient experts explained that members of the same family may have the condition. Patients have

often been carers for their parents, and they may also be concerned about their children developing the condition in the future.

- 4.3 The condition places a significant burden on family members because they provide physical and emotional care to patients while experiencing a considerable emotional burden of their own. Carers of people with hATTR amyloidosis reported that dealing with gastrointestinal problems (especially diarrhoea), patients' mental functioning and the combination of symptoms is particularly difficult. The committee concluded that hATTR amyloidosis is a rare, serious and debilitating condition that severely affects the lives of patients, families and carers.

## Unmet need

- 4.4 The clinical experts explained that hATTR amyloidosis is a progressive and relentless condition and, at the time of the evaluation, no treatments were available to treat the underlying cause. The condition is usually not diagnosed immediately because different symptoms may appear at different times for each individual; a delay of 4 years from the first symptoms appearing to getting a diagnosis is typical. As a result, at the time of diagnosis, the condition is likely to be advanced and the survival rate poor. Patient experts also explained that they have mixed experiences of disease management approaches, and that new treatments offer considerable hope to them and to their families. Patients and carers value efficacy, convenience and a low risk of side effects. The clinical experts also expected that better communication and predictive testing would help to diagnose the condition earlier. Patients might be able to fully recover if a disease-modifying treatment was available. The committee recognised that there is a significant unmet need for effective treatment options for hATTR amyloidosis.

## Impact of the new technology

### Clinical evidence

- 4.5 The committee discussed the clinical evidence available for patisiran:

- APOLLO (n=225), a randomised controlled trial that assessed the efficacy and safety of patisiran (n=148) compared with placebo (n=77) over 18 months. Results were reported overall and by subgroups (including cardiac involvement and genotype).
- A single-arm phase 2 open-label extension (OLE) study (n=27) that assessed the safety and tolerability of patisiran for up to 36 months. It captured data about patients who enrolled in a previous phase 2 open-label dose escalation study.
- Global OLE (n=211), an ongoing single-arm open-label study assessing the long-term efficacy and safety of patisiran for up to 48 months. It is capturing data on patients from APOLLO (n=186) and the phase 2 OLE (n=25), and is estimated to complete in July 2019.

The committee noted that APOLLO and Global OLE included people from the UK, and that the most common mutations seen in UK clinical practice were represented in the trials (see [section 2.2](#)). It also noted the view of the clinical experts that the trials were generalisable to clinical practice in the UK. The ERG explained that, in APOLLO, there was an unexpected imbalance in dropouts between groups; a larger proportion of patients in the placebo arm stopped treatment (38%) compared with patients in the patisiran arm (7%). The clinical experts explained that they would expect the stopping rate to be higher in the placebo arm compared with the patisiran arm because adverse events linked to disease progression would be expected to be more frequent. The ERG also noted that a greater proportion of patients had cardiac involvement in the patisiran arm (61%) than the placebo arm (47%). The company highlighted that this would potentially have biased the results against patisiran. The committee concluded that the clinical evidence was broadly generalisable to NHS clinical practice.

## Study outcomes

- 4.6 The committee was aware that, in APOLLO, the primary outcome was the mean change from baseline in neurological impairment measured by the modified Neuropathy Impairment Score +7 (mNIS+7) at 18 months. The clinical experts

explained that mNIS+7 is a composite measure of neurological impairment including motor, sensory and autonomic polyneuropathy assessment. A decrease in mNIS+7 score indicates an improvement in symptoms. Other outcomes collected in the trial included the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) questionnaire, the European Quality of Life-5 Dimensions (EQ-5D-5L) questionnaire, assessment of serum transthyretin (TTR) levels and assessment of cardiac function (through echocardiogram and cardiac biomarkers such as troponin I and N-terminal pro-B-type natriuretic peptide [NT-proBNP]). Additional outcomes were motor strength, disability, gait speed, nutritional status, symptoms of autonomic and peripheral neuropathy, large and small nerve fibre function, grip strength, blood pressure, and ambulation (assessed using familial amyloidotic polyneuropathy [FAP] stages and polyneuropathy disability [PND] scores). Most outcomes were measured at baseline and 18 months; some were also measured at 9 months.

- 4.7 The committee discussed whether the outcomes captured all aspects of the condition. The clinical experts explained that hATTR amyloidosis is a systemic condition and its main features are peripheral neuropathy, and autonomic and cardiac symptoms (see [sections 2.2 and 2.3](#)). They further explained that mNIS+7 is a comprehensive measure of neurological impairment that has been specifically modified from the original NIS+7. It was modified to better characterise and quantify sensory function at multiple sites, autonomic function and nerve conduction changes associated with progression of hATTR amyloidosis. The committee was aware that the Norfolk QoL-DN was developed in people with diabetes. However, the clinical experts explained that the autonomic symptoms seen in diabetes, such as gastrointestinal symptoms, are similar to those seen in hATTR amyloidosis. They further explained that NT-proBNP is a good marker of heart function and correlates with cardiac symptoms in patients with hATTR amyloidosis and that, to a certain extent, the EQ-5D-5L captures pain and fatigue. The clinical and patient experts agreed that there was a good correlation between improvement in peripheral neuropathy and autonomic symptoms. However, these can improve at different rates, and some aspects of the condition are difficult to measure because their effect on quality of life is subjective. The committee therefore concluded that the outcomes measured in APOLLO likely captured most of the aspects of the condition important to people with hATTR amyloidosis.

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## APOLLO results

4.8 There was a statistically significant difference in favour of patisiran between the patisiran and placebo groups in change from baseline in mNIS+7 score. Patients in the placebo group had a worse score and patients in the patisiran group had a better score (the least squares mean [LSM] difference between groups was -16.0 points at 9 months,  $p < 0.001$ ; and -34.0 points at 18 months,  $p < 0.001$ ). The treatment effect was statistically significant in all components of the mNIS+7 score and all subgroups (see [section 4.5](#)). The committee was aware that a 2-point change is considered the minimum clinically important difference (MCID), based on a consensus report from the International Peripheral Nerve Society for the original NIS score. The mean maximum TTR reduction over 18 months was 87.8% in the patisiran group but only 5.7% in the placebo group. During consultation, clinical experts explained that the likelihood of halting or reversing amyloid deposition, and so reducing neuropathy and improving cardiac function, is dependent upon the extent of reduction in TTR. There is no threshold for an effect. The effect of a given reduction will vary from person to person because of differences in turnover and production of TTR. However, the clinical experts' view was that most patients would derive clinically meaningful benefit with a reduction of more than 80%. There was a statistically significant difference in favour of patisiran between the patisiran and placebo groups in change from baseline in Norfolk QoL-DN score at 18 months; patients in the placebo group worsened and those in the patisiran group slightly improved (LSM difference between groups: -21.1,  $p < 0.001$ ). No MCID for the Norfolk QoL-DN has been reported in the literature. Cardiac outcomes were shown to improve more in the patisiran group compared with placebo at 18 months on most outcomes assessed, including left ventricular wall thickness (LSM difference between groups 0.9 mm,  $p = 0.02$ ) and global longitudinal strain (LSM difference between groups 1.37%,  $p = 0.02$ ). The difference between patisiran and placebo group in EQ-5D-5L was 0.09 points at 9 months (95% confidence interval [CI] 0.05 to 0.14) and 0.20 points (95% CI 0.15 to 0.25) at 18 months. The patient experts explained that the benefits seen in the trial translated into a marked effect on patients' lives. For example, after having patisiran, some people reported regaining a social life, not having to wear incontinence pads and being able to go to a restaurant without worrying about debilitating bowel symptoms. Another patient who has had patisiran for 4.5 years has started to walk again and is now back at work full time. The clinical experts described that a reduction of amyloid deposits in organs has been seen in the

medical imaging of some patients. This, together with the APOLLO results and other improvements in some of the patients they see in clinical practice, persuaded them that patisiran could provide compelling benefits. They added that the effect was expected to increase over the time patients have patisiran. This is because, while TTR production is suppressed, the body is able to clear accumulated amyloid deposits. The committee therefore concluded that the evidence showed that patisiran offers considerable benefit for patients and that, in addition to stopping disease progression, patisiran has the potential to reverse it.

## Long-term benefits of patisiran

- 4.9 The committee recalled that APOLLO collected data for up to 18 months and Global OLE was ongoing and collecting efficacy and safety data for up to 5 years. The company presented the interim data cut at 52 weeks, at which time patients had had treatment with patisiran for up to 48 months. The ERG noted that these data should be interpreted with caution because they included patients who had had treatment with patisiran for different durations, depending on when they entered the study. The committee was also aware that patisiran has been available through the Early Access to Medicines Scheme and that the company intended to release data collected as part of this in the next 12 months. Clinical experts advised that the clinical benefits of patisiran seem to be maintained in patients who have been having treatment for 5 years. The committee concluded that there was no long-term clinical evidence available for patisiran, but future benefits could be greater than what was presented to the committee.

## Starting and stopping patisiran treatment

- 4.10 The marketing authorisation for patisiran states that it is indicated for treating hATTR amyloidosis at FAP stages 1 and 2. The clinical experts explained that this reflected the APOLLO trial and means that people with no symptoms would not be treated. The summary of product characteristics for patisiran does not explicitly discuss when it is appropriate to stop treatment with patisiran. According to clinical experts, the main circumstance in which it might be appropriate to stop treatment is if TTR reduction is not maintained. However, the

clinical experts noted that their experience and expectation was that very few people would stop the drug. NHS England stated that treatment should stop when the condition progress to FAP stage 3 (see [table 1](#)) as per the marketing authorisation. The committee concluded that it was only able to appraise patisiran within its marketing authorisation, that is when patisiran treatment is started when the condition is in FAP stages 1 and 2, and stopped when the condition progresses to FAP stage 3.

## Adverse events

4.11 The proportion of patients with adverse events in APOLLO was high (97%) in both arms, but most events were mild or moderate. Thirteen deaths occurred (n=7 patisiran; n=6 placebo) but none were causally related to patisiran. In patients who continued having patisiran in Global OLE, it was well tolerated for up to 48 months. The committee discussed premedication treatments (needed before having patisiran infusions) but was assured by the clinical experts that they expected risks associated with these treatments to be low. It noted that patisiran has a favourable safety profile with a low stopping rate and that there had been no adverse events involving glomerulonephritis. The committee concluded that the adverse events associated with patisiran are manageable.

## Cost to the NHS and value for money

### Company's economic model

4.12 The company presented a Markov model, in which patients could move through 12 alive health states defined by a combination of the severity of their polyneuropathy (PND score) and cardiomyopathy (NT-proBNP). Patients could transition from PND 0 to PND IV (see [table 1](#)). Additionally, patients in each PND stage were stratified by NT-proBNP score (a value above 3,000 pg/ml denoting cardiac involvement). The model included an additional state for death. Patients could enter the model in any health state except PND 0. The company explained the health states were based on PND and NT-proBNP scores (rather than the APOLLO primary outcome mNIS+7) because there were data relating the PND

score and NT-proBNP to survival that were not available for mNIS+7. The company preferred health states based on PND score, arguing that it provides a more granular assessment of the condition than FAP stage (because it has more levels of change in disease severity). The ERG noted that a model defined by PND and NT-proBNP scores, but which excludes states or events associated with other key aspects of the condition (such as autonomic dysfunction), would introduce uncertainty around the expected cost effectiveness of patisiran. The ERG further explained that, compared with a model defined by PND scores, fewer health states would be needed in a model defined by FAP stage. It added that, consequently, less manipulation of the available APOLLO data would be needed but that it may result in a model less sensitive to changes in patients' underlying health states. The clinical experts highlighted that changes in mobility are correlated with change in cardiac function and autonomic neuropathy, so are indirectly predictive of harm and death. Despite this, the committee was concerned that the model relied on an assumed correlation between PND score and factors that patients have identified as particularly important, such as autonomic dysfunction and mortality (see [section 4.7](#)). The committee considered that, although the model structure was broadly reasonable, it did not capture all aspects of the condition, so was unlikely to reflect the true expected cost effectiveness. It concluded that it would take this into account in its decision making.

## Modelling starting and stopping patisiran treatment

- 4.13 The marketing authorisation states that patisiran is indicated for hATTR amyloidosis in adults with stage FAP stages 1 or 2. In the company's updated model, patients who reached PND IV (FAP stage 3) immediately stopped patisiran and subsequently had best supportive care (BSC). The committee acknowledged that, in addition, a stopping rule using data from APOLLO was also implemented, meaning that patients could stop in any health state based on a log-normal time-to-treatment discontinuation curve. The ERG explained that implementing both approaches at the same time may have overestimated the stopping rate. However, the committee noted that it had had a minimal effect on the incremental cost-effectiveness ratio (ICER). The committee also heard from clinical experts that very few patients in the trial stopped treatment, so the derived discontinuation function would largely have been based on stopping treatment



for other reasons than reaching PND IV. It agreed that there were some uncertainties in the company's updated assumption, but understood that implementing the subsequent rules had a relatively small effect on the ICER. It therefore accepted the model for decision making.

## Transition matrices used for modelling disease progression

4.14 Patients transitioned between PND health states according to 2 matrices, using a 6-month cycle. The initial matrix was derived from transitions seen in the relevant arm of APOLLO and was used for the first 3 cycles. During subsequent cycles, patients having patisiran were assumed to follow the same transition probabilities as in the first 3 cycles. However, a different approach was used to model movement of patients having BSC. It was assumed that they could either stay in their current health state or progress to the next worst PND state during each cycle, but not move to an improved health state. This matrix was derived from the probability that a patient's PND state worsened between baseline and 18 months in the placebo group of APOLLO, and the estimated probability of crossing the NT-proBNP threshold of 3,000 pg/ml or more during any given 6-month cycle. The ERG noted that the method used to convert 18-month data from APOLLO to 6-month cycles was inappropriate. This was because there were more than 2 health states and the population in each health state was sparse, and because it produced a small bias in favour of BSC. It also noted that, although 9-month timepoint was not a pre-specified final endpoint assessment, it may have been informative (for NT-proBNP) to use because it would have provided additional information to the model and may have produced a different extrapolation across the PND scores. Furthermore, the matrices would not have needed any adjustment if a longer cycle duration had been selected. The committee concluded that the company's method of modelling of health-state transitions introduced uncertainty into the model, especially for the extrapolated period for which no long-term data exists (see [section 4.9](#)). However, it was aware that this had little effect on the cost effectiveness.

## Health-state utilities used in the model

4.15 The company used the EQ-5D-5L utility values collected in APOLLO mapped to

EQ-5D-3L (using Van Hout et al. 2012) for a regression model relating quality of life to PND score and the interaction of time by treatment. Utilities for patients having patisiran and BSC were the same at baseline, but increased every month for patients having patisiran and decreased every month for patients having BSC (utilities and regression parameters are considered confidential by the company and cannot be reported). The company capped the utility values so that they could not exceed a maximum (patisiran) or fall below a minimum (BSC) in each health state. It applied a further cap to ensure that the utilities for each health state did not exceed those for the general population in England (using data from Kind et al. 1999). The ERG considered the regression to be unreliable because it:

- excluded important parameters (such as cardiac involvement)
- included the interaction of time by treatment without the main terms (that is, time and treatment)
- chose the minimum and maximum caps arbitrarily, which would not have been needed if the model had been correctly specified.

During consultation, the company submitted a revised base case that relied on a regression model including all regression terms (that is, treatment group, time, PND score, NT-ProBNP, and the interaction of time by treatment) but still relied on the use of maximum and minimum caps. The ERG explained that, without the minimum and maximum caps, the utilities reached unrealistic values. For example, over time, patients with PND II in the patisiran arm were assumed to have the same utility as patients with PND 0 (that is, no symptoms) although this affected only very few patients. The committee noted that a utility could vary within the same health state depending on treatment group. The company explained that this was because PND score does not reflect all aspects of the condition; people may be in the same PND state but have improved autonomic symptoms if they are taking patisiran. The committee considered that this was at odds with what it had heard from clinical experts about improvements in polyneuropathy and autonomic symptoms being correlated (see [section 4.7](#)). It questioned the reliability of the original and revised methods to generate the utilities and considered that it was unlikely that someone with no symptoms would have the same utility as someone with PND II. During consultation, the company provided a post-hoc mixed model of repeated measures of APOLLO's key outcomes (including

EQ-5D, COMPASS-31, Norfolk QoL-DN); this showed that utilities can improve (patisiran) or decrease (BSC) within the same PND health state from baseline to 18 months. After 18 months, because neither of the mixed model curves (based on observed APOLLO data) was approaching a plateau by trial end, the company extrapolated the utilities based on time-dependent effect. Following consultation, the company also explored scenario analyses in which the minimum and maximum caps were removed and any improvement in quality of life within a given PND stage was limited by time (see [section 4.22](#)). It explored the limitation of treatment benefit based on arbitrary timepoints: 4, 5 and 7 years. The company considered the scenario analyses to be conservative because the utility associated with BSC treatment group in a given PND state could not worsen, which is clinically implausible. The ERG explored further timepoints (2, 3, and 6 years) to assess the effect on cost effectiveness. The committee was satisfied with the assumptions of the scenario analyses (that is, no minimum and maximum caps and treatment benefit limited by time) and considered which timepoint for the duration of treatment benefit would be most appropriate. The ERG explained that, in both the original and revised model, constraints in minimum and maximum caps overrode the regression equation outputs at approximately 5 to 6 years. The committee concluded that the appropriate timepoint from which treatment benefit would be limited was 5 years, and that this was also in line with clinical experience with patisiran.

## Health-state utilities captured in the model after stopping treatment

- 4.16 The company used a formal stopping rule, and added a time-to-treatment discontinuation function (see [section 4.13](#)) to its model. The ERG had concerns about the modelling of utility values for patients who had stopped treatment. It explained that, to correctly implement the assumptions about patient utility (that is, no immediate utility rebound after stopping), the model would need to track patient utility at the point patisiran is stopped. This would mean that, for someone stopping patisiran, utility would increase for a period, plateau and then, after stopping, would decrease for a period and then plateau. For patients stopping sooner, there would not be the initial plateau. The ERG explained that, to properly

account for utility values that are dependent on the time of stopping, the model would need to track patients separately according to the time point at which they stopped. However, the company's simple Markov model was not designed to accommodate this. The ERG suggested the use of tunnel states or patient-level simulation. The committee understood that modelling utility after stopping treatment introduced uncertainty into the model. It also recalled that it had a minimal effect on the ICER (see section 4.13). The committee concluded that it would take this into account in its decision making.

## Gastrointestinal-related disutilities

4.17 The company's model included time- and state-dependent utilities based on a regression model fitted to EQ-5D data from APOLLO (see [section 4.15](#)). Its revised base case also included an additional assumption in which patients with PND above 1 in the BSC group incurred further time-independent gastrointestinal (GI)-related disutilities. The committee recalled that the model might not have captured all aspects of the condition, including autonomic dysfunction, which patients have identified as a particularly important aspect of the condition. However, the clinical experts described it as an aspect that is difficult to measure (see sections [4.7](#) and [4.12](#)). It understood from the company that the additional change was meant to reflect the different genetic mutations seen in APOLLO from those seen in routine UK clinical practice. This meant that the model underestimated the benefit of patisiran on autonomic neuropathy (a determinative feature of the condition) as captured by GI dysfunction. The committee discussed the genetic mutations of patients seen in APOLLO and recalled that the trial was broadly generalisable to UK clinical practice (see [section 4.5](#)). Clinical experts explained that, in most cases, the underlying causes of death in hATTR amyloidosis are a combination of autonomic neuropathy (which includes the severely affected GI tract) and cardiac involvement. The clinical experts noted that people with Val30Met mutation (a large proportion of those in APOLLO) have relatively homogenous symptoms, usually developing autonomic disease later in the course of the condition but without much cardiac involvement. They also explained that, in the UK, a high proportion of people have Thr60Ala mutation, which can be characterised by peripheral neuropathy, autonomic neuropathy and cardiac involvement. Therefore, the people recruited into APOLLO differed from people seen in the UK because they had relatively

little autonomic neuropathy. The ERG highlighted that an earlier approach used by the company to model improvement (patisiran) or worsening (BSC) in EQ-5D within each PND health state with time was an attempt to reflect the aspects of the condition not captured in the definition of model health states. Therefore, if the inclusion of further GI-related disutilities in the model was also intended to quantify those factors, it was unclear what the time-dependent utilities were intended to reflect. The committee noted the ERG's critique but acknowledged the importance of fully capturing GI dysfunction in the model. However, it noted that it had not been presented with any quantitative data showing a low incidence of GI symptoms in people in APOLLO, as might be suggested by the range of mutations in patients studied.

- 4.18 The company pointed out that it is possible that not all aspects of autonomic neuropathy were captured in the model. It explained that the generic EQ-5D questionnaire might have functional limitations. This meant that the effects of GI dysfunction or improvement might not have been captured fully by the assessment. The committee also heard patient testimony illustrating ways in which EQ-5D might not capture GI dysfunction properly (for example, low blood pressure, sweating, waking up several times during the night because of irregular bowel movement). The ERG had concerns about the company's argument explaining that the questionnaire has been routinely used in functional bowel disease and other serious GI-related conditions before, and has also been used to measure autonomic neuropathy. It clarified that the questionnaire should be fully sensitive to capture the effect of such symptoms on quality of life. The committee understood that additional GI-related disutilities may conceptually overlap with those captured by the EQ-5D questionnaire. It agreed that it was not clear what was being taken into account by the separate disutility and what was reflected in the utilities already. It considered that including the additional GI disutility raised the possibility of double-counting the effect of autonomic dysfunction, but that the EQ-5D questionnaire might not fully capture all the effects of autonomic neuropathy. The committee therefore concluded that the true value was somewhere between the model outcomes with and without the additional disutility.
- 4.19 The committee understood that, in the patients in the updated model, stopping patisiran treatment and moving to BSC did not immediately incur the full GI-related disutilities. It heard from the company that it is unlikely that patients

would accrue all the disability and symptoms immediately after stopping treatment, so the disutility was increased gradually, only reaching 100% at 5 years. The ERG raised a concern that the gradual onset of GI-related disutilities should have been applied to all patients having BSC, including those who did not previously have treatment with patisiran. It also pointed out that the actual calculations coded in the model were unclear, and it was concerned that the additional disutility remained constant at 10% of the full amount, rather than increased gradually. The committee understood that applying disutility for people stopping patisiran had a relatively small effect on the ICER. It also considered the ERG's scenario analysis in which GI-related disutilities were applied immediately for people stopping treatment and for BSC. The committee concluded that the ERG's assumption was preferable for use in the model.

## Caregiver disutilities applied in the model

4.20 The company included a disutility for carers of 0.01 for patients with PND IV. The committee questioned whether this adequately reflected the carer burden reported in the Amyloidosis Research Consortium UK survey (see [section 4.2](#)). The committee considered that the way the company had modelled utility was highly uncertain, and that the alternative source suggested by the ERG was equally flawed. In its revised base case, the company assumed 1 full-time caregiver in FAP stages 1 and 2, and 2 full-time caregivers in FAP stage 3 reflecting the additional care needs of people with more advanced disease. This was in line with what the committee had accepted in [NICE's highly specialised technology guidance on inotersen](#). The committee concluded it was satisfied with the company's updated model incorporation of revised caregiver disutilities.

## Modelling effects of patisiran and BSC on mortality

4.21 Mortality was modelled based on a series of hazard ratios to population death rates and relied on the assumption that mortality risk increases with advancing neuropathy (PND score) and cardiac involvement (NT-proBNP). It was largely based on external data, with hazard ratios for NT-proBNP and PND scores extracted from Gillmore et al. (1998) and Suhr et al. (1994) respectively, and assumed to act independently. The ERG questioned the relevance of the Suhr

study because the population was not clearly defined and there was uncertainty about the survival analysis. It advised that the company's approach was convoluted, circular and uncertain but agreed there was no other existing source available linking PND stage and mortality. The company explained that it did not use APOLLO data to estimate mortality parameters because of the limited number of deaths. However, the ERG noted that the company did not attempt to supplement the limited APOLLO data with experts' beliefs. The clinical experts agreed with the company's approach of combining both the effect of neuropathy and cardiac involvement. They explained that patients can die from either complications of cardiac involvement or complications of neuropathy, which are captured in part by the PND state, although the prognosis is affected more by cardiac involvement. They noted that the hazard ratios for each PND/NT-proBNP combination were largely plausible. In its preferred analysis, the ERG assessed the effect of removing the mortality effect in patients with no cardiac involvement. In its revised base case, the company assessed the effect of removing mortality associated with PND score in all patients. The committee considered this to be unrealistic based on the testimony from clinical experts that increased PND score is likely to be associated with increased mortality risks. The committee recognised the complexities of the company's approach, which combined both PND and cardiac mortality, and its limitations. However, it concluded that this approach was acceptable because of the lack of other evidence.

- 4.22 After consultation, the company implemented a new approach by modelling the effects of treatment with patisiran and BSC on mortality using NT-proBNP alone. The ERG argued that this method may be flawed because it suggested that undiscounted survival of people in the BSC group increased to 14.43 years, which was not in keeping with the bounds suggested by clinical experts. This contrasts with the original company model in which it was only 8.27 years. In addition, the ERG described the substantial effect of the new assumption on the ICER, which fell considerably as people spent more time in the BSC arm of the model accruing negative quality-adjusted life years (QALYs) after 2 years. The clinical experts suggested that the biggest determinant of mortality is whether the heart is involved or not. Survival of patients with cardiac involvement is usually 2 to 5 years. It understood that survival can depend on genotype. Median survival in people with the Thr60Ala mutation (seen commonly in the UK) has been reported to be 64 months, while people with Val30Met mutation can live for up to

10 years. The committee considered whether longer survival might be expected in the model because of the younger age of patients starting treatment. However, the clinical experts explained that age does not have a major effect on survival, even though hATTR amyloidosis is now likely to be diagnosed earlier (people are usually diagnosed before the age of 60 to 65 years). They inferred that, unlike stage of disease at the time of diagnosis, age at diagnosis is not a very important factor. The committee considered that it was unlikely that the model reflected the natural history of the condition in the UK, and that the 14.43 years of survival on BSC was not credible. It therefore concluded that life expectancy in the new model was outside expectations, even considering the possible age difference between UK patients and those in the model and the possibility that patients may now be diagnosed earlier.

- 4.23 In an exploratory analysis, the ERG showed the effect of using PND-related hazard ratios only. This was in line with what was accepted in [NICE's highly specialised technology guidance on inotersen](#). The committee recalled that, for most genotypes, there is a combination of neuropathy (PND stage) and cardiomyopathy (see [section 4.7](#)), and that the clinical experts had advised that progression of these was correlated. It therefore considered that using PND mortality hazard ratios would capture the excess mortality caused by cardiomyopathy. It recognised that, while mortality based on PND hazard ratios is less than ideal, it could not accept the company's new analysis. This was because it lacked face validity and was not in line with the natural history of the condition in the UK. The committee understood that there were advantages and disadvantages with each source of mortality data. It also recognised the uncertainties around the values but concluded that the use of PND-related mortality only, although not optimal, was acceptable for decision making.

## Resource use

- 4.24 The company used a Delphi approach to elicit experts' beliefs about resource use, in particular for cardiomyopathy-related costs. The ERG was concerned that the method is unlikely to have reflected the true expected cost and uncertainty. Moreover, the company included the costs of adverse events by assuming a constant rate of events (based on APOLLO) as well as a reduction over time (based on treatment discontinuation function; see [section 4.13](#)). The ERG



considered that this was illogical because it meant that all patients would stop patisiran at the end of the time horizon and, at the same time, develop adverse events. Additionally, the committee was aware that the company proposed a homecare service for patients and noted that the costs for this were not included in its model. The committee concluded that there were some uncertainties in the company's resource use assumptions, and that it would take this into account in its decision making.

## Discount rate

4.25 The committee was aware that [NICE's guide to the methods of technology appraisal \(2013\)](#) and its [interim process and methods of the highly specialised technologies programme \(2017\)](#) specify that the discount rate that should be used in the reference case is 3.5% for costs and health effects. However, it also states that a non-reference-case rate of 1.5% for costs and health effects may be used when: treatment restores people to full or near-full health when they would otherwise die or have severely impaired lives; if it is highly likely that there will be long-term benefits (normally sustained for at least 30 years); and if the treatment does not commit the NHS to significant irrecoverable costs. The company proposed using a discount rate of 1.5% on health effects and 3.5% on costs because it argued patisiran has shown long-term benefit and has shown the ability to halt or reverse disease progression. It accepted that patisiran was unlikely to meet the requirement that health benefits must be sustained over at least 30 years. However, it considered that this criterion unfairly penalises people with hATTR amyloidosis because they are older and so would have a life expectancy of less than 30 years even in the absence of this condition. The committee discussed the company's arguments for applying the 1.5% discount rates to health effects only and noted that:

- Neither the NICE Reference Case nor the cited non-reference case support the use of differential discount rates (that is 1.5% for health outcome and 3.5% for costs, or vice-versa).
- The clinical experts explained that, based on response to chemotherapy in light chain amyloidosis (the most common form of systemic amyloidosis), they expected only around half of people remaining on treatment to return to what might be considered near-full health. This is because the condition is

often diagnosed at an advanced stage from which it may not be possible to return to PND 0 or FAP 0.

- Whether health benefits are sustained for 30 years is considered only because cost-effectiveness analyses are particularly sensitive to the choice of discount rate when benefits are accrued over a very long time. The criterion does not therefore penalise people with hATTR amyloidosis because of the age at which they are diagnosed.

The committee therefore concluded that patisiran does not meet the criteria for applying a discount rate of 1.5%. It concluded that a discount rate of 3.5% should be applied for both costs and health effects.

## Cost-effectiveness results

4.26 The committee noted that, in the company's base case, patisiran was associated with an ICER of £80,730 per QALY gained. However, it considered that the company's base case was not appropriate for decision making. This was mainly because of concerns about the utility values used in the model and survival output produced by the model. The committee therefore considered the ICER per QALY gained using its preferred assumptions, which were:

- accepting the company's formal stopping rule and the additional time-to-treatment discontinuation curve (see [section 4.13](#))
- capping duration of treatment-related utility gains or losses within the same health state at 5 years (see [section 4.15](#))
- using a utility cap for the general population based on more recent data (Ara and Brazier 2010, rather than Kind et al. 1999 – see [section 4.15](#))
- applying only part of GI-related disutilities in the model (see [section 4.18](#))
- applying GI-related disutilities immediately after stopping treatment with patisiran (see [section 4.19](#))
- assuming 1 carer assumed in FAP stages 1 and 2, and 2 carers in FAP stage 3 based on the company's updated model (see [section 4.20](#))

- modelling effects of treatment on mortality using PND-related hazard ratios only (see [section 4.23](#))
- using a discount rate of 3.5% for costs and benefits (see [section 4.25](#)).

A scenario provided by the ERG, which used the committee's preferred assumptions and applied more pessimistic gastrointestinal-related disutilities in the model, resulted in survival output that was more plausible. In this scenario analysis patisiran was associated with an ICER of £125,256 per QALY gained. The committee acknowledged that neither the company's base case nor the ERG scenario were without flaws. However, it considered that the most plausible ICER for patisiran compared with BSC using the confidential commercial arrangement for patisiran was likely to be between £80,730 and £125,256 per QALY gained. Therefore, the committee concluded that the most plausible ICER is above the range that can usually be considered an effective use of NHS resources for highly specialised technologies.

## Application of QALY weighting

4.27 The committee understood that [NICE's interim process and methods of the highly specialised technologies programme \(2017\)](#) specifies that a most plausible ICER of below £100,000 per QALY gained for a highly specialised technology is normally considered an effective use of NHS resources. For a most plausible ICER above £100,000 per QALY gained, judgements about the acceptability of the highly specialised technology as an effective use of NHS resources must take account of the magnitude of the incremental therapeutic improvement, as revealed through the number of additional QALYs gained and by applying a 'QALY weight'. It understood that a weight between 1 and 3 can be applied when the QALY gain is between 10 and 30 QALYs. The committee discussed the QALY gains associated with patisiran and highlighted that these were likely to be just below 10 (ranging from 9.16 QALYs using the committee's preferred assumptions to 12.19 QALYs in the company's revised base case, but expected to be closer to the lower end point). Although, QALY gains with patisiran were likely to be close to the threshold, the committee concluded that patisiran did not meet the criteria for applying a QALY weight.

## Impact of the technology beyond direct health benefits and on the delivery of the specialised service

- 4.28 The committee discussed the effects of patisiran beyond its direct health benefits and the testimony of the patient experts. It understood from patient and clinical experts that all aspects of patients', families' and carers' lives are affected by the condition. It noted that there is a significant negative financial effect for families if they have to give up work to provide full-time care or need to employ professional carers. The patient experts explained that patisiran has changed their experience of living with hATTR amyloidosis. The committee concluded that hATTR amyloidosis affects patients beyond direct health benefits.
- 4.29 The committee noted that hATTR amyloidosis is managed at the National Amyloidosis Centre, so no additional infrastructure or staff training will be needed to manage patisiran use in England.

## Additional factors

### Innovation

- 4.30 The committee discussed the innovative nature of patisiran. It noted that the drug is the first licensed 'small interfering ribonucleic acid (RNA)'. It also noted that confirmation of the clinical utility of RNA interference in this case opens up the possibility of applying similar strategies for muting genes in a range of conditions. Patisiran's mechanism of action is distinct from all previous treatments for hATTR amyloidosis and produces a substantial reduction or 'knockdown' in TTR protein. The company considered that patisiran is a step-change in managing hATTR amyloidosis because it is likely to provide great benefit in terms of halting or reversing disease progression. The patient experts explained that having treatments available would give people with the condition hope of stabilisation and possibly reversal of the condition, both for themselves and for family members who may be affected in the future. The clinical experts explained that patisiran has a favourable safety profile and is well tolerated. The committee concluded that the benefits of patisiran showed that it is a unique and innovative treatment.

## Uncaptured health-related benefits

- 4.31 The committee considered whether there were any health-related benefits that were not captured in the economic analysis. It was aware that hATTR amyloidosis is a devastating condition that affects patients as well as their families and carers. The committee acknowledged that there were uncaptured health-related benefits that could be realised with long-term patisiran treatment (see [section 4.9](#)). It recognised the severity of the condition and the importance of generating potentially life-long health benefits for this patient population. The committee also understood that patients would highly value treatments that could help to stop or reverse the condition in the longer term. The committee noted the innovative mechanism of action, the degree of TTR 'knockdown' achieved, and the clinical expectation that this stops disease progression and may allow the condition to be reversed in some patients. This would enable patients to return to work, carry out daily activities, participate in a more active family and social life; and maintain their independence and dignity. Therefore, it was persuaded that there were health-related benefits that were not captured in the company's model, which needed to be accounted for in its decision making.
- 4.32 The committee acknowledged that hATTR amyloidosis is an exceptionally rare condition that causes a wide variety of symptoms and impairments. The condition has a considerable effect on patients' independence and dignity, and their ability to work, take part in family and social life, and carry out daily activities. The condition is progressive, and can result in death from its effects and complications within 5 to 15 years of the first symptoms developing. The clinical experts emphasised the importance of cardiac disease because it is the main cause of mortality and of autonomic neuropathy because of its major effect on quality of life.

## Equality

- 4.33 The committee noted the potential equality issue raised by clinical experts and the company, and recognised that specific mutations were more common in some ethnic groups in the UK. It also considered whether the age of onset of the condition raised particular issues of equality. The committee concluded that its recommendations apply equally, regardless of age or ethnicity, so a difference in

disease prevalence in different age and ethnic groups does not in itself represent an equality issue.

## Conclusion

- 4.34 The committee noted that the clinical evidence suggested that patisiran provides considerable clinical benefits in terms of stopping disease progression and potentially reversing the condition in the longer term. It considered that the new RNA-interference method of action was innovative and first of its kind. This aspect alone would not have been enough for the committee to recommend patisiran as an option for treating hATTR amyloidosis. However, taken together with other factors, the committee considered that it was a relevant aspect. Also, it acknowledged that additional benefits not captured in the economic modelling are likely to be realised with long-term treatment with patisiran. The committee considered the strengths and weaknesses of the company's base case and the ERG's scenario analyses, noting the overall uncertainty in the model. Having considered the ICERs from both approaches, the committee agreed that the most plausible ICER for patisiran compared with BSC was likely to be somewhere between £80,730 and £125,256 per QALY gained (see [section 4.26](#)). This is above what would normally be considered value for money within the context of a highly specialised service.
- 4.35 The committee discussed the need to balance the importance of improving the lives of people with hATTR amyloidosis and their families. It noted [NICE's social value judgements: principles for the development of NICE guidance](#), which emphasises the importance of considering the distribution of health resources fairly within society as a whole, as well as considering factors other than relative costs and benefits alone. When developing the social value judgements, the [Citizens Council](#) considered that rarity alone is not a mitigating factor for accepting high ICERs, but that the committee should consider taking into account other factors such as disease severity in its decision making. The committee concluded that the severity of hATTR amyloidosis should be considered in its decision making.

## Additional factors taken into consideration in the decision

## making

4.36 The committee was aware of the uncertainty around the ICER for patisiran. However, it acknowledged that there were additional factors that should be taken into consideration in its decision making, including:

- the rarity and severity of the condition (see [sections 4.1 and 4.2](#))
- the considerable effect on families and carers (see [section 4.3](#))
- the size of the health benefits (see [sections 4.8 and 4.9](#))
- the innovative nature of the treatment and health-related benefits not captured in the economic model (see [section 4.30](#) and [sections 4.31 and 4.32](#)).

The committee concluded that, considering all these factors, it was able to recommend patisiran as an option for treating hATTR amyloidosis.

## 5 Implementation

- 5.1 Section 8(6) of the [National Institute for Health and Care Excellence \(Constitution and Functions\)](#) and the [Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication. Because patisiran has been available through the [early access to medicines scheme](#), NHS England and commissioning groups have agreed to provide funding to implement this guidance 30 days after publication.
- 5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE highly specialised technologies guidance. When a NICE highly specialised technologies guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final evaluation document.
- 5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has hereditary transthyretin amyloidosis with stage 1 and stage 2 polyneuropathy and the doctor responsible for their care thinks that patisiran is the right treatment, it should be available for use, in line with NICE's recommendations.



## 6 Evaluation committee members and NICE project team

### Evaluation committee members

The highly specialised technologies evaluation committee is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered that there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

### NICE project team

Each highly specialised technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

#### **Orsolya Balogh and Aminata Thiam**

Technical leads

#### **Richard Diaz, Ian Watson, Ross Dent and Eleanor Donegan**

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#### **Joanne Ekeledo**

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