

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Evaluation consultation document

# Patisiran for treating hereditary transthyretin- related amyloidosis

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using patisiran in the context of national commissioning by NHS England. The highly specialised technologies evaluation committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts, patient experts and NHS England.

**This document has been prepared for consultation with the consultees.** It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the committee. NICE invites comments from the consultees and commentators for this evaluation and the public. This document should be read along with the evidence (see the [committee papers](#)).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of the criteria considered by the committee, and the clinical and economic considerations reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance on the use of patisiran in the context of national commissioning by NHS England?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

**Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.**

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final evaluation document.
- Subject to any appeal by consultees, the final evaluation document may be used as the basis for NICE's guidance on using patisiran in the context of national commissioning by NHS England.

For further details, see the [interim process and methods of the highly specialised technologies programme](#).

**The key dates for this evaluation are:**

Closing date for comments: 9 January 2019

Second evaluation committee meeting: 12 February 2019

Details of membership of the evaluation committee are given in section 6.

**Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.**

## **1 Recommendations**

- 1.1 Patisiran is not recommended, within its marketing authorisation, for treating hereditary transthyretin-related amyloidosis in adults.
- 1.2 This recommendation is not intended to affect treatment with patisiran that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

### **Why the committee made these recommendations**

Hereditary transthyretin-related amyloidosis is a rare condition that severely affects the quality of life of people with the condition, their families and carers. Current treatment is supportive care.

Clinical trial evidence shows that patisiran reduces disability and increases quality of life. It may provide long-term benefits, but evidence for this is lacking.

There are uncertainties in the economic modelling. It captures some important aspects of the condition but not all the more subjective symptoms. Also, the cost effectiveness estimates for patisiran are much higher than what NICE considers acceptable for highly specialised technologies.

Patisiran reduces disability and increases quality of life and is innovative. But it does not appear to provide value for money in the context of a

highly specialised service. Patisiran is therefore not recommended for routine funding in the NHS.

## 2 The condition

2.1 Hereditary transthyretin-related (hATTR) amyloidosis is an ultra-rare condition caused by inherited mutations in the 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. Affected systems 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.

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). The FAP stage also captures elements of autonomic neuropathy and is used in the marketing authorisation for patisiran. The description and correspondence between PND scores and FAP stages is reported in Table 1.

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

<b>PND score</b>	<b>PND score description</b>	<b>FAP stage</b>	<b>FAP stage description</b>
<b>0</b>	No impairment	<b>0</b>	No symptoms
<b>I</b>	Sensory disturbances, preserved walking capability	<b>1</b>	Unimpaired ambulation; mostly mild sensory and motor neuropathy in the lower limbs and autonomic neuropathy
<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

<b>IIIA</b>	Walking only with the help of 1 stick or crutch		progression to the lower limbs, upper limbs and trunk
<b>IIIB</b>	Walking with the help of 2 sticks or crutches		
<b>IV</b>	Confined to a wheelchair or bedridden	<b>3</b>	Wheelchair-bound or bedridden; severe sensory and motor neuropathy of all limbs, and autonomic neuropathy
Abbreviations: FAP, familial amyloidotic polyneuropathy; PND, polyneuropathy disability			

2.4 People may mainly have symptoms of polyneuropathy or cardiomyopathy, but most patients seen in the NHS will have symptoms of both over the course of the condition. In the UK, the most common genetic mutations associated with both 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 evidence submission, there were thought to be around 150 people with hATTR amyloidosis in the UK.

2.6 Current treatment options for people with hATTR amyloidosis are limited. They mainly focus on symptom relief and supportive care including pain management, nutritional and mobility support, and lessening the effects of the condition on other organs (for example, pacemakers, arrhythmia management). There are no disease-modifying treatments available for people with hATTR amyloidosis that is being treated in the NHS. 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.

2.7 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 disease, and outcomes are poor in people with cardiac involvement, so it is rarely done in England.

- 2.8 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.

### **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, which would apply if the technology had been recommended. 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-related (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; 38% of patients in the survey reported having faecal or urinary incontinence that

considerably impairs their quality of life. Symptoms may severely affect professional and social life. The patient experts explained that the condition may affect many members of the same family. 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 currently there are no treatments available to treat the underlying cause. The condition is usually not diagnosed immediately; there is typically a delay of 4 years from the first symptoms appearing to getting a diagnosis. 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 symptom and 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. However, they are likely to accept risks if they are outweighed by treatment benefit. 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 mutations seen in UK clinical practice were well represented in the trials (see section 0). It also noted the view of the clinical experts that the trials were generalisable to clinical practice in England. 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 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 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 FAP stages and 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, and to capture gastrointestinal dysfunction. 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 explained that some aspects of the condition are difficult to measure because their effect on quality of life is subjective. They agreed that there was a good correlation between improvement in peripheral neuropathy and autonomic symptoms. The committee concluded that the outcomes measured in APOLLO captured most of the aspects of the condition that are important to people with hATTR amyloidosis.

### **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 slightly 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 TTR reduction over 18 months was 87.8% in the patisiran group which was above the threshold of 80.0% that clinical experts advised was needed to halt or reverse neuropathic progression; it was 5.7% in the placebo group. There was a statistically significant difference in favour of patisiran between the patisiran and placebo groups in change from baseline on 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 all 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 concluded that the evidence showed that patisiran offers considerable benefit for some patients.

### **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. However 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. The committee concluded that there was no long-term clinical evidence available for patisiran, but further data were being accumulated.

### **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. The clinical experts noted that it was their experience and expectation that very few people would stop the drug. The main circumstance in which it might be appropriate to do so was if TTR reduction was not maintained. NHS England stated that it interpreted the wording of the marketing authorisation to mean that treatment should stop when the condition progress to FAP stage 3 (see Table 1). The clinical experts commented that, in the absence of explicit commissioning criteria stating otherwise, they would not want to stop treatment if the condition reached FAP stage 3 and patients were considered to still be benefitting from treatment. The committee concluded that patisiran would be started in people with FAP stages 1 and 2, and that clinicians would continue to consider using the treatment as long as patients continued to benefit.

### **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. 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. The ERG explained that PND is not the best overall descriptor of the condition because it only captures mobility impairment (see Table 1); a model based on FAP stage would have also captured the autonomic symptoms. The company argued that PND provides a more granular assessment of the condition than FAP (because it has more stages for symptomatic patients). The clinical experts highlighted that changes in mobility are correlated with shifts in cardiac function and autonomic neuropathy so, although PND score is based on mobility impairment, it is 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 will take this into account in its decision making.

### **Modelling starting and stopping patisiran treatment**

4.13 The committee was aware that APOLLO (which feeds into the economic model) included a patient at FAP stage 3. Because the marketing authorisation specifies patients should have FAP stages 1 or 2 when treatment starts (see section 4.10), in its preferred analysis, the ERG explored what effect removing this patient would have on the cost effectiveness. The company's model did not include a formal stopping rule so patients could continue treatment indefinitely, reflecting the marketing authorisation (see section 4.10). A discontinuation curve was applied to reflect some patients stopping over time because of, for example, adverse events. However it was assumed that patients would continue to have treatment in FAP stage 3 (corresponding to PND IV; see Table 1). The committee concluded that the starting and stopping rules applied in the model broadly reflected the way clinicians would interpret the marketing authorisation for patisiran.

### **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 best supportive care (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 because there were more than 2 health states, and that this produced a small bias in favour of BSC. It also noted that it may have been informative to use a 9-month time point (for NT-proBNP). 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).

### **Health-state utilities**

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.

The company explained that the results of the model had face validity



because they reflected the decreasing quality of life in patients having BSC and the increasing quality of life in people having patisiran seen over time in APOLLO. However, 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). 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 method 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. The ERG provided a scenario analysis in which the utility values did not change over time, effectively meaning that they were the same for each health state regardless of treatment. It also explored the effect of using other sources of utilities on the cost-effectiveness estimates. In particular, it used a study by Stewart et al. (2017), which reported utilities according to FAP stage (for Val30Met mutations and 'other mutations' categories) valued using Brazilian tariffs. However, the committee was concerned that the Brazilian tariffs were very different from UK-specific tariffs, so reflected different cultural views and societal preferences. In addition, 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. It concluded that an alternative

modelling approach may have resulted in utility values with greater face validity.

## **Mortality**

4.16 Mortality was modelled based on a series of hazard ratios 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 PND score and NT-proBNP 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 explained that the company's approach was convoluted, circular and uncertain but agreed there was no other existing source available. 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 polyneuropathy and cardiac involvement, and explained that patients usually die from cardiac complications. They noted that the hazard ratios for each PND/NT-proBNP combination were largely plausible. In its preferred analysis, the ERG assessed the impact of removing the mortality effect in patients with no cardiac involvement. The committee recognised the complexities of the company's approach and its limitations, but concluded that this approach was acceptable because of the lack of other evidence.

## **Resource use**

4.17 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

4.18 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 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.
- Patisiran may be expected to provide long-term benefits but there were many remaining uncertainties that prevented the committee concluding that long-term health benefits were likely to be achieved.

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.

### **Other assumptions**

4.19 The ERG highlighted several additional assumptions and parameters that were uncertain and that it had addressed in its preferred analysis. In particular, in the company's analysis:

- the administration and premedication costs had not been adjusted by treatment compliance
- one-off costs associated with progression of polyneuropathy had been double-counted

- patisiran cost-savings had been double-counted by applying a treatment discontinuation function as well as a compliance rate.

The ERG also recalculated the starting health-state distribution in the model according to the baseline data for PND and NT-proBNP in APOLLO. The committee considered the ERG's assumptions to be appropriate.

### Cost-effectiveness results

4.20 The committee considered the results of the economic analysis, taking into account the company's base case and the ERG's preferred analysis and exploratory scenarios. In the company's base case, patisiran was associated with quality-adjusted life year (QALY) gains of 8.30 and an incremental cost-effectiveness ratio (ICER) above £100,000 per QALY gained compared with BSC (the ICER is considered confidential by the company and cannot be reported here). In the ERG's preferred analysis, patisiran was associated with QALY gains of 6.85 and an ICER above £100,000 per QALY gained compared with BSC. The ERG's preferred analysis:

- corrected errors in the company's model (see section 4.19)
- used a discount rate of 3.5% for costs and benefits (see section 4.18)
- recalculated starting state distribution and removed a patient with FAP stage 3 (see sections 4.19 and 4.13)
- used a utility cap for the general population based on more recent data (Ara and Brazier, 2010, rather than Kind et al., 1999)
- removed the mortality effect for lower NT-proBNP states (see section 4.16).

4.21 The committee reiterated its views on the unreliability of the utility estimates and considered an ERG's exploratory scenario in which the change of utility over time was removed (see section 4.15). This scenario led to a substantial increase in the ICER compared with the ERG's

preferred analysis ICER. The committee concluded that the most plausible ICER was likely to lie between the ERG's preferred analysis and the scenario in which the change in utility over time was removed. Both ICERs were substantially higher than the range that can be considered an effective use of NHS resources for highly specialised technologies.

### Application of QALY weighting

4.22 The committee understood that the [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 below 10 (8.30) in the company's base case, the ERG's preferred analysis (6.85) and the ERG's exploratory analysis in which utility was constant over time (3.97). The committee concluded that there was no evidence to suggest that patisiran would meet the criteria for applying a QALY weight.

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

4.23 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, but that quantifying this was difficult. It concluded that it was highly unlikely that the effects would be sufficient to overcome its concerns about the difference between the preferred ICER and values considered an effective use of NHS resources for highly specialised technologies.

- 4.24 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.

### ***Other factors***

- 4.25 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.
- 4.26 The committee discussed the innovative nature of patisiran, noting that it is the first licensed ‘small interfering ribonucleic acid’. Therefore, its mechanism of action is distinct from all previous treatments for hATTR amyloidosis. The company considered that patisiran is a step-change in managing hATTR amyloidosis because it may dramatically improve people’s lives by slowing disease progression. The patient experts explained that having a treatment available would give people with the condition hope – both for themselves and for family members who may be affected in the future. The committee concluded that patisiran is innovative.

## Managed access

4.27 The committee reiterated the uncertainties associated with patisiran. It recalled that, although the clinical evidence might be associated with uncertainties, it was satisfied that the trial outcomes captured the main aspects of the condition, that is, peripheral neuropathy, and autonomic and cardiac symptoms (see section 4.7). It also considered that patisiran provides considerable clinical benefit. However, the committee considered that the company's model, defined by a combination of the severity of polyneuropathy (PND score) and cardiomyopathy (NT-proBNP), did not adequately capture all aspects of the condition (including autonomic symptoms) that the clinical and patient experts considered to be a major part of hATTR amyloidosis. The committee explained that this had led to an inaccurate reflection of the true expected cost effectiveness (see section 4.12). It therefore noted that further data collection, as proposed in a managed access arrangement, would not be a possible route to resolving the key uncertainties associated with patisiran because it would not address the uncertainties in the economic model. The committee acknowledged that long-term data were already being collected and would be made available in the future (see section 4.9). It concluded that patisiran could not be recommended and that a managed access arrangement would be unlikely to resolve the uncertainties.

## Conclusion

4.28 The committee acknowledged that hATTR amyloidosis is an exceptionally rare condition that causes a wide variety of symptoms and impairments, and has a serious and substantial effect on the quality of life of patients, and their families and carers. It was aware that the clinical trials captured most aspects of the condition, that is, peripheral neuropathy, and autonomic and cardiac symptoms. It noted that the clinical evidence suggested that patisiran provides considerable clinical benefits. However, it considered that these clinical benefits were not appropriately represented in the economic model because the model structure was



based on a combination of polyneuropathy and cardiomyopathy, and did not capture autonomic symptoms. In addition, the company's approach to modelling utility was highly uncertain and the resulting utility values lacked face validity. The committee considered that the most plausible ICER lies between the ERG's preferred analysis and the exploratory scenario in which utilities did not change over time. Both of these ICERs were above the range that can be considered an appropriate use of NHS resources for highly specialised technologies. It also noted that patisiran did not meet the criteria for QALY weighting to be applied, and that there remained important uncertainties within the economic model. The committee therefore did not recommend patisiran as an option for treating hATTR amyloidosis.

## **5 Proposed date for review of guidance**

- 5.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Peter Jackson

Chair, highly specialised technologies evaluation committee

December 2018

## 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.

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Technical Lead

#### **Ian Watson, Ross Dent**

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Project Manager

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