NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final evaluation document

Inotersen for treating hereditary transthyretin-related amyloidosis

1 Recommendations

1.1 Inotersen is recommended, within its marketing authorisation, as an option for treating stage 1 and stage 2 polyneuropathy in adults with hereditary transthyretin-related amyloidosis. It is recommended only if the company provides inotersen according to the commercial arrangement (see section 3).

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, and their families and carers. Current treatment is supportive care.

Clinical trial evidence shows that inotersen slows progression of the disease considerably, although its long-term benefits are uncertain. Some assumptions in the economic modelling are also uncertain, particularly around the utility values and the healthcare costs. Despite the uncertainties, inotersen is likely to provide important clinical benefits for people with hereditary transthyretin-related amyloidosis and value for money within the context of a highly specialised service. It is therefore recommended for use in the NHS.

2 The condition

2.1 Hereditary transthyretin-related (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

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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 affecting 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 company's evidence submission, there were thought to be around 150 people with hATTR amyloidosis in the UK.

2.3 Neuropathy in hATTR amyloidosis can be classified according to walking ability (described by Coutinho et al.1980):

- Stage 1: people do not need help with walking and have mostly mild sensory and motor neuropathy in the lower limbs, and autonomic neuropathy.
- Stage 2: people need help with walking, there is progression of neuropathy in the lower limbs and symptoms develop in the hands (weakness and muscle wasting).
- Stage 3: people are wheelchair bound or bedridden and have severe sensory and motor neuropathy of all limbs, and autonomic neuropathy.

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 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

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the condition on other organs (for example, pacemakers, arrhythmia management). There are no disease-modifying treatments 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.

2.6 Liver transplant, which prevents additional amyloid deposits forming, 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.

2.7 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.

3 The technology

3.1 Inotersen (Tegsedi, Akcea Therapeutics) is a novel, first-in-class 2'-O-2-methoxyethyl phosphorothioate antisense oligonucleotide that inhibits production of transthyretin (TTR) in adults with hereditary transthyretin-related (hATTR) amyloidosis. Inotersen has a marketing authorisation for 'the treatment of stage 1 or stage 2 polyneuropathy in adults with hATTR amyloidosis'.

3.2 The most frequent adverse reaction listed in the summary of product characteristics is injection site reactions (50.9%). Other commonly reported adverse reactions are nausea (31.3%), anaemia (27.7%), headache (23.2%), pyrexia (19.6%), peripheral oedema (18.8%), chills (17.9%), vomiting (15.2%), thrombocytopenia (13.4%) and decreased platelet count (10.7%). In the main clinical trial for inotersen (the NEURO-TTR study) there was 1 death, which was considered to be related to

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inotersen. The main safety concerns with inotersen treatment are glomerulonephritis and thrombocytopenia, therefore enhanced monitoring (platelet count, urine protein to creatinine ratio and estimated glomerular filtration rate [eGFR]) has been implemented. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.3 Inotersen is self-administered once weekly by subcutaneous injection. The price of inotersen per weekly dose (284 mg) is £5,925 (excluding VAT; company submission). The company has a commercial arrangement. This makes inotersen 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 7) considered evidence submitted by Akcea Therapeutics, 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

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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 fecal or urinary incontinence that considerably impairs their quality of life. Symptoms may severely affect patient's professional and social lives. 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, a delay of 4 years from the first symptoms appearing to

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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 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 side effects 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 company's clinical evidence came from 2 studies:

- NEURO-TTR was a double-blind, randomised, placebo-controlled study which assessed the efficacy of inotersen (n=113) compared with placebo (n=60) when administered for 65 weeks (15 months). After NEURO-TTR ended, patients could enter the extension study for long-term follow up. Also, patients on placebo could switch to treatment with inotersen.
- The NEURO-TTR Extension study was an open-label study that evaluated the long-term efficacy and safety of inotersen. A total of 135 patients were enrolled in the open-label extension. Some information about the extension study is considered academic in confidence by the company, so cannot be presented here.

The committee discussed the generalisability of the trials. It acknowledged that 6 patients in NEURO-TTR were recruited from the UK. It also discussed the genetic mutations of patients in the trials and in UK clinical practice. The committee understood that the most common genetic

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mutations in patients in NEURO-TTR were Val30Met (52%), Thr60Ala (13%) and Leu58His (6%), which the clinical experts considered to reflect those usually seen in the UK (see section 2.4). The ERG noted that patients in the inotersen arm had had cardiomyopathy symptoms for longer (45 months) than those in the placebo arm (34 months). The company highlighted that this would potentially have biased the results against inotersen. The committee therefore concluded that the trial population was generalisable to patients in UK clinical practice. It also understood the limitations of developing an evidence base for an ultra-rare condition and was satisfied that it had been presented with the best available evidence.

Study outcomes

4.6 The primary outcomes in NEURO-TTR were mean change from baseline in neurological impairment as measured by the modified Neuropathy Impairment Score +7 (mNIS+7) and the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) score at 15 months. The mNIS+7 is a composite measure of neurological impairment including motor, sensory and autonomic polyneuropathy assessment. Norfolk QoL-DN is a patient-reported measure validated in patients with hATTR amyloidosis with polyneuropathy. It is designed to capture the effect of neuropathy on quality of life. A decrease in mNIS+7 score indicates a reduction in neurological impairment and a decrease in Norfolk QoL-DN total score indicates an improvement in quality of life. Other outcomes included the assessment of serum transthyretin (TTR) levels, neurological impairment, cardiac function, autonomic function, weight loss, motor function, quality of life and safety. The company explained that the studies were powered to detect changes in both primary outcomes.

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 section 2.2). They further explained that mNIS+7 is a comprehensive measure of neurological

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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. The committee acknowledged that it was difficult to capture all aspects of a condition that has such a big impact on patients. But it concluded that the outcome measures used in the clinical trial captured the condition reasonably well and included most aspects of importance to patients.

NEURO-TTR study results

4.8 During the 15 months of the NEURO-TTR study, a statistically significant difference in favour of inotersen was seen, that is, there was a slower rate of disease progression in patients who had inotersen than in patients who had placebo. The mean increase from baseline in the mNIS+7 composite score in the placebo arm was 24.9 compared with 4.2 in the inotersen arm at week 66. The least squares mean difference between groups was 19.73 points ($p<0.001$). The difference was statistically significant in all components of the mNIS+7 score and for the subgroups analysed. The committee was aware that a 2-point change was considered the minimum clinically important difference, based on a consensus report of the Peripheral Nerve Society. For the Norfolk QoL-DN score at 15 months, there was little change from baseline in the inotersen arm (−0.08), but an increase of 10.8 was seen in the placebo arm (least squares mean difference between arms of 11.68, $p<0.001$). No minimal clinically important difference for the Norfolk QoL-DN is reported in the literature. Patient experts noted that slowing disease progression is of value to them and their families and carers because without treatment, progression to the later, debilitating stages of the disease can be rapid. Therefore to

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remain in the earlier stages of the disease, with a better quality of life, for longer, would benefit patients and their families and carers. But the ERG explained that no evidence was provided suggesting that inotersen completely stops peripheral neuropathy in hATTR amyloidosis. Inotersen greatly slowed the progression of neuropathy but did not reverse the disease. During consultation the company submitted further clinical data from the NEURO-TTR Extension study on people who had inotersen for up to 104 weeks (2 years). It stated that the results showed the benefit of inotersen is maintained for at least 2 years. The company acknowledged that the data from the extension study do not prove that the disease is halted or reversed after taking inotersen for 104 weeks, but it maintained that for some people this was plausible. The committee concluded that the evidence showed that inotersen had considerable benefit in slowing disease progression, but it did not stop progression.

4.9 The mean serum TTR reduction over 15 months exceeded 70% in the inotersen group, ranging from 68.41% in week 13 to 74.03% in week 65. In the placebo group, mean serum TTR decreased by 8.5% in week 3 and then remained constant throughout the study period. Differences in least squares means between the arms for change in serum TTR level from baseline were statistically significant ($p<0.001$) at all time points. The clinical experts expressed their view that serum TTR reduction is the preferred surrogate marker for amyloidosis and they considered this to be an important indicator of disease response to treatment. They also stated that, in general, people whose serum TTR level decreased by 80% have a better prognosis than people who have smaller reductions in serum TTR levels. During consultation, clinicians further explained that a greater decrease in serum TTR level is likely to give greater benefit in halting or reversing progression of the disease. They accepted that using a binary 80% value as a criterion for long-term clinical benefits has not been validated and the effect of reducing serum TTR levels would vary among patients because of differences in turnover and production of amyloid in the body. The clinical experts explained that some people may still have

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benefit when serum TTR levels are reduced by less than 80%. However, they agreed that there is a strong correlation between low serum TTR level and halting or reversing the disease. Therefore a higher reduction in serum TTR levels is preferred. The committee concluded that although inotersen did not decrease serum TTR level by 80%, it provided clinical benefit.

Long-term benefits of inotersen

4.10 The main clinical trial providing evidence for inotersen was 15 months long. The committee also considered results from the extension study (see section 4.8). It discussed the likelihood of inotersen being beneficial for a longer period of time and its effects on disease progression. The clinical experts explained that, based on other forms of amyloidosis, if production of amyloid protein is stopped, clearance of amyloid deposits from the organs can lead to improvements in clinical outcomes, although this can take many years. Reducing serum TTR is considered to predict such improvement. The committee recalled that serum TTR was reduced by about 70% in patients on inotersen treatment (see section 4.9) in the clinical trial. This was less than the optimal percentage suggested by the clinical experts, and it therefore noted that long-term clearance of amyloid may not be achieved. The committee noted that further data were collected in the extension study but concluded that there was still insufficient evidence on the long-term benefits of inotersen. It therefore remained uncertain whether the clinical benefit would be maintained in the long term.

Adverse events

4.11 Treatment-emergent adverse events were seen in almost all patients in NEURO-TTR. Most of these events were mild or moderate. Five deaths occurred in the inotersen arm and 1 death (from intracranial haemorrhage caused by severe thrombocytopenia [a reduced number of blood platelets]) was considered to be related to the study drug. There were no deaths in the placebo arm. After monitoring of platelet levels was

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implemented (see section 3.2), no other severe thrombocytopenia events occurred in NEURO-TTR. The company and clinical experts explained that platelet numbers may reduce gradually in some people who have inotersen and sudden falls are not expected. Therefore, monitoring every other week is appropriate. People whose platelets decrease may have their dose of inotersen reduced by increasing the interval between doses but are expected to be able to return to the licensed dosing schedule when their platelets increase. The committee also understood that in the clinical trial people accepted the increased monitoring because it allowed them to stay on inotersen. The committee acknowledged that the major safety risks associated with inotersen can be effectively managed with routine monitoring in clinical practice. Therefore, it concluded that inotersen has an acceptable safety profile.

Cost to the NHS and value for money

Economic model

4.12 The company did a de novo cost-effectiveness analysis comparing inotersen with best supportive care. The cost-effectiveness results were estimated using a cohort-based Markov state transition model. The Coutinho et al. disease staging system (see section 2.3) was used to define health states 1 to 3 and the model also incorporated a death state. Transitions between disease stages were modelled independently for each model arm. It was assumed that people cannot move back from stage 3 to stages 1 and 2. A lifetime time horizon (41 years) was adopted to fully capture the effect of the disease and mortality, and a cycle length of 4 weeks was modelled. The company explained that the choice of model structure was based on a model submitted to the Advisory Group for National Specialised Services for a closely related disease area (tafamidis for the treatment of transthyretin amyloidosis in adults with stage 1 symptomatic polyneuropathy). The committee was satisfied that the model structure reflected the course of the condition.

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Starting and stopping treatment

4.13 In the model people could start treatment in either stage 1 or stage 2, and treatment was assumed to stop when people have stage 3 disease. The committee noted that this was in line with inotersen's marketing authorisation; inotersen is indicated for stage 1 and stage 2 polyneuropathy in adults with hereditary transthyretin amyloidosis. The clinical experts explained that if a patient continues to benefit from treatment, both patients and clinicians would be reluctant to stop treatment in stage 3. The main reason for stopping treatment might be if serum TTR reduction was not maintained. The committee reiterated that it was only able to make recommendations within inotersen's marketing authorisation. NHS England stated that because of the wording of the marketing authorisation, treatment would not likely be funded when the condition progresses to stage 3. The committee acknowledged that the stopping rule applied in the model may not reflect how clinicians would prefer to use the treatment. It agreed that inotersen would be started when the disease is in stage 1 or 2 and would be stopped when the condition progresses to stage 3.

4.14 The clinical experts stated that the stopping rate in clinical practice is unknown. In the company's model, survival curves for time to discontinuation were fitted to data from the NEURO-TTR and NEURO-TTR Extension studies. The committee agreed that the most reasonable extrapolation curve would allow for a persistent but decreasing rate of stopping treatment over time. Therefore, it preferred the log-logistic curve. The clinical experts agreed that they would expect only a small number of people to stop inotersen, and that the rate was likely to be higher in the first months and then decrease over time. During consultation, the company updated its base case using the committee's preferred curve. The committee agreed with the approach in the updated company model.

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Disease progression in the company's model

4.15 In the company's model, people moved between stages using the transition probabilities based on observations from the NEURO-TTR study up to week 66. Transition probabilities from 35 to 66 weeks were used to extrapolate beyond 66 weeks in both arms. After consultation, the company updated its model so that it was not possible to move from stage 2 to stage 1 during the extrapolated phase in the best supportive care arm. The company explained that a placebo effect during the trial period allowing a slight increase in quality of life was possible, but that it was implausible that someone on best supportive care would have a substantial increase in quality of life after 66 weeks of decline. The committee concluded that it was satisfied with the company's revised approach to modelling disease progression.

Mortality

4.16 Parameters used to inform mortality in the original model were based on a Delphi panel of 4 clinical experts. The clinical experts explained that the hazard ratios for mortality in the model appeared plausible but acknowledged the considerable uncertainty around these parameters because they were based on expert opinion rather than published data. The committee agreed that the hazard ratios were highly uncertain and therefore preferred to see scenario analyses using lower hazard ratios in the model. After consultation, the company updated the hazard ratios in its base-case model, applying values of 2.01 for stage 1, 2.42 for stage 2 and 9.53 for stage 3 (Suhr et al. 1994). The committee concluded that the updated hazard ratios for mortality better reflected the risk associated with having the condition and it was satisfied with the revised approach.

Carers

4.17 In its original base case, the company assumed that every patient had 2 full-time carers in each stage of the condition. The patient experts explained how important carers are for people with hATTR amyloidosis. The committee noted that people in stage 1 need minimal support from

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carers, but the need for support gradually increases in stage 2. However, 24-hour care is essential in stage 3 because of immobility and possible loss of eyesight, combined with other symptoms such as incontinence. The patient experts explained that as the condition progresses relatives who provide care may not be able to provide sufficient support, and therefore professional carers are needed. Clinical experts explained that this is the picture for most people in the severe disease stage, and that multiple carers are needed to provide round the clock care. The ERG explained that it was appropriate to consider carer disutility in the model, but because people with hATTR amyloidosis spend most time in the stage 1 and stage 2 health states in the model, assuming 2 full-time carers throughout the entire model period was inappropriate. After consultation, the company revised its base-case analysis to assume that people need 1 carer in stages 1 and 2, but need 2 carers in stage 3, reflecting the additional care needs of people with more advanced disease. The company justified the change by providing results of its own survey of 36 carers of people with hATTR. Carer testimonies showed that they spend a substantial amount of time providing care (on average 43 hours per week in stage 1, 81 hours in stage 2 and 87 hours in stage 3). The committee accepted the company's revised approach and concluded that it was appropriate to assume 1 carer in stages 1 and 2, and 2 carers in stage 3 of the model.

Adverse event utilities and costs in the model

4.18 The committee discussed uncertainties around the utilities and costs of adverse events in the model. It understood that the company considered most of the adverse events to be mild (serious adverse events occurred in less than 5% of people in the trial) or manageable by increased monitoring. Therefore it did not include utility decrements or costs associated with the most serious adverse events in the model. In an exploratory analysis the ERG applied disutilities and costs associated with adverse events in the model. The ERG explained that the changes did not have a major effect on the incremental cost-effectiveness ratio (ICER).

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However, the committee concluded that for clarity it would prefer disutilities and costs of adverse events to be included in the model. After consultation the company included these changes and these were accepted by the committee.

Source of utility data

4.19 The company stated that there were no algorithms to map Norfolk QoL-DN to the EQ-5D, therefore published literature was used for health state utilities in the model. In its original model, the company used the utilities from a study by Stewart et al. (2017), which reports utilities according to Coutinho stages (for Val30Met mutations and 'other mutations') using a Brazilian value set. The ERG argued that using EQ-5D values based on Brazilian general population preferences was questionable because there are important differences in preferences for health states between the UK and the Brazilian populations. The ERG noted when people responded to the EQ-5D questionnaire for any level 3 response, a decrement was applied in the UK value set but it was not applied in the Brazilian value set, meaning that poorer health states are valued much lower in the UK tariffs than in the Brazilian tariffs. The committee concluded that the utility values used in the model were highly uncertain.

4.20 The company explained that utility values estimated by applying the UK tariff to the raw EQ-5D response data from the THAOS registry (a global, multicentre, longitudinal observational registry for all patients with hATTR amyloidosis) would have been preferred. But the company advised that this registry is owned by another company and it had not been possible to secure access to these data.

4.21 The committee discussed the alternative utility sources used in the ERG's exploratory analyses. In particular, a study by Faria et al. (2012), which reported utility values by disease stage as used in the tafamidis appraisal (see section 4.12). The committee understood that utilities from Faria et al. were based on mapping total quality of life data (based on defined total quality of life score cut-offs on the Norfolk QoL-DN questionnaire) to the

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EQ-5D. The ERG explained that the lowest possible EQ-5D based utility was above 0, and therefore utility gains might be underestimated with this method. Alternatively, the SF-36 data from NEURO-TTR could be mapped to EQ-5D but this would only provide utility values for stages 1 and 2.

4.22 After consultation the company implemented a new approach to model health-related quality of life. It generated utilities that would be close to the values that might be obtained if raw data from the preferred THAOS registry were available. The company's new approach used 1 or 2 EQ-5D health states in which the values from the Brazilian data were closest to the mean disease stage values for patients in the THAOS registry. The ERG argued that this method was uncertain, explaining that it did not account for variability in people's preferences within the UK and Brazilian data sets. Also, the ERG described that implausible health state classifications were generated with the new approach. One of the states selected for mapping utility in stage 3 disease specified no problems with self-care. The committee understood that this was unlikely to reflect the health status of someone with stage 3 disease. The ERG therefore preferred the linear mapping function described by Faria et al. (see section 4.21). The committee acknowledged the company's comments that the linear approach was not statistically meaningful because of unequal variability in the data. The company also explained that linear mapping was not suitable because the condition is categorised by 3 stages, therefore the data cannot be considered linear. The committee noted that the new method introduced uncertainty into the model because it could generate implausible health state classifications. It understood that there were advantages and disadvantages with each source of utility data, and recognised the uncertainties around the utility values used in the updated company model. Because the preferred raw EQ-5D data were not available, the committee concluded that the company's revised approach to modelling health-related quality of life, although not optimal, was acceptable for decision making.

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Health state utilities

4.23 After consultation, the company varied the utility values in both model arms depending on the time spent in each health state. Utilities increased in every cycle for people having inotersen and decreased in every cycle for people having best supportive care if they remained in the same health state. The company capped the utility values so that they could not exceed a maximum or fall below a minimum 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 Ara and Brazier, 2010) and did not fall below the utility of the next worst stage. The committee concluded that introducing time-dependent utilities in the company's base case was acceptable.

Resource use

4.24 After consultation the company replaced the healthcare resource use costs in the best supportive care arm with publicly available data, sourced from UK clinicians and costed using UK national average unit cost information. The company made changes to the costs applied to each stage and reduced the inotersen health state costs by 43% for stages 1 and 2 only. The company explained that this approach reflects the expected substantial improvement in healthcare resource use costs for people on inotersen within each stage. The ERG explained that there were some errors in how these were implemented in the model, but this had minimal impact on the ICER. The committee concluded that there were some uncertainties in the company's resource use assumptions but accepted the updated model for 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, they also state that a non-reference-case rate of 1.5%

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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, in its original base case, incorporated a discount rate of 1.5% for costs and health effects. It justified this change from the reference case, stating that the benefits of treatment were expected to be substantial and sustained over a lifetime. Firstly, the committee recalled its discussions around long-term benefits and its conclusion that it remained uncertain whether the clinical benefit seen would be maintained in the long term. Secondly, it did not consider that there was enough evidence to conclude that people who had treatment would be considered to have 'normal or near-normal health'. This is because people are often diagnosed at an advanced stage of disease and because inotersen slows, but does not stop, disease progression. Thirdly, the committee accepted that inotersen 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 without this condition. The committee noted that the criterion that health benefits must be sustained for 30 years is included when deciding whether a lower discount rate can be justified 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 there was no justification for changing from the reference case discount rate of 3.5% for costs and health effects. At consultation, the company amended its economic model to reflect the committee's preference.

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Cost-effectiveness results

4.26 The committee considered the results of the economic analysis, taking into account the company's updated base case, and the ERG's exploratory scenario analyses. The committee accepted most of the company's revisions, which gave an ICER of £150,636 per quality-adjusted life year (QALY) gained for inotersen compared with best supportive care. The company's revisions incorporated these assumptions:

- Treatment with inotersen stops when disease progresses to stage 3 (see section 4.13).
- Discontinuation was modelled using a log-logistic curve (see section 4.14).
- People on best supportive care cannot move from stage 2 to stage 1 after week 66 of treatment (see section 4.15).
- Mortality hazard ratios of 2.01 for stage 1, 2.42 for stage 2 and 9.53 for stage 3 (see section 4.16).
- 1 carer assumed in stages 1 and 2, and 2 carers assumed in stage 3 based on the company's updated model (see section 4.17).
- Amendments to the costs and disutility of adverse events applied (see section 4.18).
- Brazilian THAOS values converted to UK utility tariffs, which were used as the source of utility values in the model (see section 4.22).
- Varying health state utility values in both model arms depending on the time spent in each health state (see section 4.23).
- Healthcare resource use costs for treating different disease stages were as used in the company's updated base case (see section 4.24).
- Costs and QALYs were discounted at 3.5% per year (see section 4.25).
- Compliance rate as used in the company's base case (information about compliance rate is considered academic in confidence by the company, therefore cannot be presented here).

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4.27 The committee understood that the company implemented most of the model changes requested during the first committee meeting (held in November 2018). It noted that after consultation, the company submitted updated evidence from the NEURO-TTR Extension study, incorporated several other model assumptions, and provided clarification as requested. The committee broadly accepted the company's revisions. But it acknowledged that substantial uncertainties remained about the source of utility values and healthcare resource use costs in the model. The committee noted that because of the outstanding uncertainties the company revised its commercial offer for inotersen, which brought the ICER down from £150,636 to £96,697 per QALY gained compared with best supportive care. Taking this into account, the committee concluded that the most plausible ICER could be considered an effective use of NHS resources for highly specialised technologies.

Application of QALY weighting

4.28 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 inotersen and highlighted that these were below 10 in the company's updated base case that was the most plausible to the committee (the exact QALY gains are considered commercial in confidence by the company, so cannot be reported here). The committee concluded that there was no evidence to suggest that inotersen would meet the criteria for applying a QALY weight.

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

4.29 The committee discussed the effects of inotersen beyond its direct health benefits and the testimony of the patient experts. It understood from patient and clinical experts that all aspects of the lives of patients, families and carers 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 inotersen has changed their experience of living with hATTR amyloidosis in a positive way. The committee recognised that inotersen has an effect beyond health benefits, but it noted that the full effect of these benefits had not been quantified. The committee considered these benefits in its decision making.

4.30 The committee noted that inotersen can be taken at home, which is an advantage for those who would find it difficult to travel to hospital. Patients or carers would need to be trained to administer the subcutaneous injections and carry out regular blood monitoring. Patients with weakness in their hands from neuropathy would need a carer or district nurse to give the medication.

Other factors

4.31 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.

4.32 The committee discussed the innovative nature of inotersen, noting that it is the first licensed 2'-O-2-methoxyethyl phosphorothioate antisense oligonucleotide and its mechanism of action is distinct from all previous

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treatments for hATTR amyloidosis. The company considered that inotersen is a step-change in managing hATTR amyloidosis. 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 inotersen is innovative.

Conclusion

4.33 The committee recognised that hATTR amyloidosis is a devastating condition, with a debilitating effect on patients and a significant emotional and financial impact on their families. It was convinced that the evidence showed inotersen slowed disease progression, which had considerable benefit to patients. But it noted that there was insufficient evidence on the long-term health benefits; patients on inotersen treatment slowly progressed to the more severe stages of the disease. Overall, the committee considered that the available evidence suggested that inotersen would provide important clinical benefits. The committee considered that the company's assumptions in the model, especially around the utility values and healthcare resource use costs, were uncertain. It also noted that inotersen did not meet the criteria for a QALY weighting to be applied. Acknowledging the uncertainties and taking into account other benefits of inotersen that were not captured in the analysis (see sections 4.29 and 4.30), the committee concluded that inotersen can be considered a cost-effective use of NHS resources for highly specialised technologies. Therefore, the committee recommended inotersen 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,

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local authorities to comply with the recommendations in this evaluation within 3 months of its date of 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-related amyloidosis and the doctor responsible for their care thinks that inotersen is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Review of guidance

6.1 The guidance on this technology will be considered for review 3 years after publication of the guidance. 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
February 2019

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7 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
Technical lead

Frances Nixon and Christian Griffiths
Technical advisers

Joanne Ekeledo
Project manager

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