NICE National Institute for Health and Care Excellence

NICE guidance

Givosiran for treating acute hepatic porphyria

Highly specialised technologies guidance
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Your responsibility

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

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

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

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

Contents

1 Recommendations

1.1 Givosiran is recommended as an option for treating acute hepatic porphyria (AHP) in adults and young people aged 12 and older, only if:

- they have clinically confirmed severe recurrent attacks (4 attacks or more within 12 months) and
- the company provides it according to the commercial arrangement.

1.2 This recommendation is not intended to affect treatment with givosiran that was started in the NHS before this guidance was published. Adults and young 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. This decision should be made jointly by the clinician, the young person and their parents or carers.

Why the committee made these recommendations

AHP is a rare, progressive and potentially life-threatening condition that can significantly affect the quality of life of people with the condition, and their families and carers. People can have acute attacks with extreme pain, nausea and fatigue, which sometimes lead to seizures and paralysis. They can also have chronic pain and fatigue. Standard treatment in the NHS is prophylactic haem arginate, which is offered to most people with recurrent severe attacks despite this use being outside its marketing authorisation.

There is no trial directly comparing givosiran with prophylactic haem arginate. However, results from clinical studies and clinical expert opinion suggest that givosiran reduces the number of acute attacks in people with AHP, as well as improving chronic symptoms and quality of life.

Some assumptions in the economic modelling are uncertain, particularly around the duration of treatment with givosiran and the effectiveness of prophylactic haem arginate. Despite this, givosiran is likely to provide important clinical benefit and improve quality of life for people with AHP. It also provides value for money within the context of a highly specialised service. Givosiran is therefore recommended for use in the NHS.

2 The condition

2.1 Acute hepatic porphyria (AHP) is a rare inherited metabolic disorder caused by a deficiency of the enzymes needed to make haem. It is characterised by high levels of porphyrin precursors, including delta-aminolevulinic acid and porphobilinogen, in the liver and other tissues. High levels of these substances damage nerve cells and can provoke acute attacks of physical pain. Acute attacks are very rare before puberty and usually start between 15 and 35 years. They are more common in women, who may be at increased risk of having an acute attack during or after pregnancy. Acute attacks are often triggered by factors such as drugs, alcohol, hormones, and infection. AHP is life-threatening because it can lead to seizures and paralysis during acute attacks. It can be debilitating in the long term because of chronic pain, fatigue, nausea and vomiting. AHP is progressive, with attack frequency and severity increasing over time. The condition varies from person to person. There are 4 types of AHP: acute intermittent porphyria, hereditary coproporphyria, variegate porphyria and aminolevulinate dehydratase porphyria. Acute intermittent porphyria is the most common form of AHP in the UK and has the highest symptom burden.

2.2 The prevalence of symptomatic AHP is estimated to be 1 in 100,000 people in Europe, which equates to about 560 people in England. Most people recover after 1 attack or a few attacks, but attacks can be recurrent in about 10% of people. People with recurrent severe attacks often have chronic symptoms and may not fully recover from an attack. According to the National Acute Porphyria Service, there are 27 people in the UK having treatment for recurrent severe attacks.

2.3 Treatment options for AHP aim to prevent attacks or manage symptoms. They include pain management, stopping medication that could have triggered symptoms, gonadotrophin releasing hormone (GnRH) analogues for hormone-induced attacks in women, and oral or intravenous glucose for acute attacks. Haem arginate is indicated for treating acute attacks of AHP. It is also used outside its marketing authorisation to prevent attacks. Liver transplant may be an option for some people with recurrent severe attacks when other treatment options have not worked.

3 The technology

3.1 Givosiran (Givlaari, Alnylam) is a small-interfering ribonucleic acid that suppresses delta-aminolevulinic acid synthase 1 production by the liver. This reduces the level of toxic precursors of porphyrin. Givosiran has a marketing authorisation in the UK for 'treating acute hepatic porphyria in adults and adolescents aged 12 years or older'. It is administered by subcutaneous injection. The recommended dose is 2.5 mg per kg body weight once a month.

3.2 Very common adverse reactions (that is, occurring in 1 in 10 people or more) include injection site reactions, nausea and fatigue. Elevated transaminases and anaphylactic reactions have led to people stopping treatment. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.3 The price for givosiran is £41,884.43 per 189 mg vial (excluding VAT; company's evidence submission). The company has a commercial arrangement. This makes givosiran 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 considered evidence submitted by Alnylam Pharmaceuticals, 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 how recurrent severe hepatic porphyria (AHP) affects all aspects of the lives of people with the condition, and their families and carers. It has a significant effect on a person's independence, their ability to work and to have a social life. People with recurrent attacks (that is, 4 or more attacks in 12 months) live in fear of having a severe attack. This can be worrying for their families and carers. Recovery from a severe attack can take a couple of months, but some people do not recover fully. The patient experts explained that even between attacks, people with recurrent severe attacks are often unable to take part in usual family and social activities because of debilitating long-term pain and fatigue. In young people with AHP, this can affect attendance at school and university. This can have a substantial emotional effect on them and their families. AHP can be life-threatening if not appropriately treated, although the clinical experts highlighted that mortality has significantly reduced since the use of haem arginate. The committee concluded that AHP is rare, serious and potentially life-threatening, affecting the lives of people with the condition, their families and carers.

Unmet need

4.2 The clinical experts explained that there is no treatment with a marketing authorisation for preventing recurrent attacks of AHP available for use in the NHS. About 95% of people have haem arginate outside its marketing authorisation to prevent recurrent attacks. But its effect reduces over time and many people still have severe attacks, needing hospital admission. According to the clinical and patient experts, haem arginate does not reduce chronic pain and fatigue. Also, it can be associated with iron overload, which can cause chronic liver inflammation. Haem arginate is given intravenously once a month but this often needs to be increased to 2 to 4 times a month. It is given through a central venous catheter, which can be difficult to maintain. The clinical experts explained that women of childbearing age could take GnRH analogues to manage hormone-induced attacks but very few chose to do so. GnRH analogues suppress ovulation and are associated with oestrogen deficiency so they are only used for up to 2 years. After this people usually have haem arginate. The clinical experts explained that previously people had a liver transplant when haem arginate was no longer an option. Although transplant can be a cure it is rarely done because of the person's health and lack of a donor organ. The clinical experts confirmed that referral for liver transplant is now often delayed in the hope that more effective and safer treatment options will become available. The committee recognised that there is a significant unmet need for effective and safe treatment options for people with recurrent acute attacks of AHP.

Diagnosis

4.3 The clinical experts explained that AHP is diagnosed by testing urine for porphobilinogen, aminolevulinic acid, and porphyrin. Given the rarity of the condition and its many non-specific symptoms, diagnosis of AHP is often delayed, or it is misdiagnosed. Genetic tests are now available. The clinical experts confirmed that these are not routinely used but help to confirm the initial diagnosis and identify the type of AHP. However, the tests do not indicate whether the condition will be severe and recurrent.

Impact of the new technology

Population

4.4 Givosiran has a marketing authorisation for treating AHP in people aged 12 and older. However, the committee noted that clinical trial evidence for givosiran from the ENVISION study (see section 4.7) is in people who had at least 2 attacks over 6 months that needed hospitalisation, an urgent healthcare visit or intravenous haem arginate. It also noted that the NICE scope for givosiran and the company evidence submission specifically defines the population eligible for givosiran as "adults and young people aged 12 years or older with recurrent severe attacks of AHP". Clinical experts explained that recurrent severe attacks are defined as 4 or more acute attacks within 12 months. Based on this, the committee concluded that the population relevant to this appraisal is adults and young people aged 12 and older with recurrent severe attacks of AHP (defined as 4 or more attacks within 12 months).

Experience with givosiran in NHS clinical practice

4.5 The clinical experts confirmed that 6 people in England have had givosiran for preventing recurrent severe attacks as part of an international clinical trial. The patient and clinical experts explained that there were minor side effects including nausea, but this only lasted for a short time. They also highlighted that givosiran reduced the frequency of attacks quickly. Attacks that did occur were less severe and people did not need hospitalisation. People still had symptoms such as chronic pain and fatigue, but this lessened with time. The committee concluded that people with AHP and their clinicians would welcome givosiran as a treatment option for preventing recurrent severe attacks.

Comparators

4.6 The company's original submission only included evidence comparing givosiran with best supportive care. This included intravenous acute haem and management of it side effects, pain medications, antiemetics, antihistamines and

antipsychotics. This was different to the NICE scope, which specified haem arginate, GnRH analogues and liver transplant as comparators. The committee recalled that prophylactic haem arginate was established NHS clinical practice for preventing recurrent acute attacks (see section 4.2). It noted that prophylactic haem arginate was used outside its marketing authorisation and referred to the highly specialised technologies interim methods and process guide. This states that comparators can be considered even though they do not have a marketing authorisation if they are part of established NHS clinical practice for the indication. The ERG explained that there is a lack of data on prophylactic haem arginate for preventing recurrent acute attacks. The clinical experts confirmed that it is challenging to collect such data in clinical practice because haem arginate is used for both prevention and acute treatment of severe attacks. The committee recalled that GnRH analogues and liver transplant are rarely used in NHS clinical practice for preventing recurrent severe attacks (see section 4.2). The committee agreed that all treatment options currently used in NHS clinical practice should have been considered. It concluded that prophylactic haem arginate is the most appropriate comparator for this appraisal. After consultation, the company submitted an economic model comparing givosiran with prophylactic haem arginate (see section 4.16).

Clinical evidence

4.7 The clinical evidence for givosiran included:

- ENVISION (n=94), a double-blind randomised placebo-controlled trial assessing the efficacy and safety of givosiran (n=48) compared with placebo (n=46). This trial was in people who had at least 2 attacks in 6 months that needed hospitalisation, an urgent healthcare visit or intravenous haem arginate. Givosiran was administered by subcutaneous injection (2.5 mg per kg body weight) once a month. After the 6-month trial period, people could join a 30-month open-label extension study (ENVISION OLE), assessing the efficacy and safety of givosiran. People could have 2 different doses of givosiran (1.25 mg per kg body weight [n=37], and 2.5 mg per kg body weight [n=56]). People in both arms also had best supportive care, which included managing chronic symptoms and acute attacks.
- A phase 1 or 2 (n=40) randomised dose-finding study that assessed the

safety of givosiran. Part C (n=17) of this study recruited people with AHP and recurrent acute attacks (that is, at least 2 attacks in 6 months that needed hospitalisation, an urgent healthcare visit or intravenous haem arginate). This part of the trial was a double-blind evaluation of 4 different doses of givosiran (n=13) compared with placebo (n=4). Follow up was 168 days.

The committee agreed that evidence from ENVISION and ENVISION OLE was relevant to this appraisal.

Generalisability of ENVISION and ENVISION OLE to NHS clinical practice

4.8 ENVISION was an international trial that included 4 people from the UK (4.3% of people enrolled). Most people had a diagnosis of acute intermittent porphyria (n=89) and only 4 people had other types of AHP. Everyone had 2 or more attacks in 6 months that needed hospitalisation, an urgent healthcare visit or intravenous haem arginate. The clinical experts confirmed that people with AHP having treatment in the NHS and for whom givosiran would be an option, have similar characteristics to people in ENVISION. The committee acknowledged that a small trial such as ENVISION may not represent the full population who would have givosiran. The clinical experts explained that best supportive care in other countries is similar to that in NHS clinical practice and it would usually include prophylactic haem arginate. This was not allowed in ENVISION. The committee concluded that people in ENVISION, other than not having prophylactic haem arginate, would have similar characteristics to those seen in NHS clinical practice.

4.9 Everyone who completed ENVISION entered ENVISION OLE. Most people (n=56) had the dose of givosiran specified in the summary of product characteristics (2.5 mg per kg body weight) but 37 people had a lower dose (1.25 mg per kg body weight). People could change between doses. The clinical experts confirmed that everyone having givosiran in the UK as part of an ongoing clinical trial has 2.5 mg per kg body weight. The committee agreed that there was some uncertainty about the generalisability of ENVISION OLE to NHS clinical practice but concluded that it was acceptable for decision making.

Study outcomes

4.10 The primary outcome of ENVISION was annualised rate of porphyria attacks (that is, attacks needing hospitalisation, an urgent healthcare visit, or intravenous haem arginate at home). At 6 months people in the givosiran arm had fewer attacks (3.2; 95% confidence interval [CI] 2.25 to 4.59) than people in the best supportive care arm (12.5; 95% CI 9.35 to 16.76). This was a relative reduction of 74% (95% CI 59% to 84%). There were fewer attacks with givosiran compared with best supportive care. The difference was smallest for attacks needing hospitalisation and was not statistically significant (relative reduction 49% 95% CI -4% to 75%). After consultation, the company submitted updated data from the latest available ENVISION OLE data-cut. These data suggested that givosiran has a sustained reduction on acute attacks up to 36 months after the start of treatment. These data are considered confidential by the company and therefore cannot be reported here. The committee concluded that givosiran was effective in reducing severe attacks compared with best supportive care.

4.11 In ENVISION health-related quality-of-life data was collected using the EuroQol 5-dimensions 5-level questionnaire (EQ-5D-5L). Results were mapped to EQ-5D-3L to obtain utility values. There was no statistically significant difference between the treatment arms at 6 months (least squares mean change from baseline in visual analogue scale: givosiran 6.8, placebo 2.8; treatment difference 4.0, 95% CI -3.3 to 11.4). The committee noted that fewer attacks did not lead to improved health-related quality of life and considered this to be unexpected. It was aware that health-related quality of life is affected by many factors including chronic symptoms and psychological factors. It recalled that chronic symptoms may not reduce as quickly as the frequency of attacks and that 6 months might be too short to capture givosiran's full benefits. The committee concluded that givosiran was likely to affect health-related quality of life but it was unclear how large such an effect would be.

Cost to the NHS and value for money

Company's model

4.12 The company's original economic model compared givosiran with best supportive care. After consultation, this was updated to compare givosiran with prophylactic haem arginate. The Markov model contained 4 health states and 1 absorbing state (death). The health states were defined by the number of severe attacks (attacks needing hospitalisation, an urgent healthcare visit or intravenous haem arginate) in 12 months:

- asymptomatic (0 attacks)
- symptomatic (1 to 4 attacks)
- recurrent (5 to 24 attacks)
- severe (more than 24 attacks).

People entered the model in the symptomatic, recurrent or severe health state. At the end of each 6-month cycle they could move to another health state, remain in the same health state or move to the absorbing state.

4.13 The hypothetical group of people in the model was assumed:

- to be 42 years at model entry
- to be 86% women and
- to have the same characteristics as people in ENVISION.

4.14 The company's economic analysis adopted an NHS perspective and had a 60-year time horizon. A discount rate of 3.5% per year was used for both costs and health outcomes. The committee was satisfied that the model structure reflected the general course of the condition.

Long-term effectiveness of givosiran

4.15 Data collected from ENVISION and ENVISION OLE during the first 18 months informed the health state of people entering the company's original model. It also informed how they moved (or transitioned) from 1 health state to another in the givosiran arm of the model. The company's base case used these transitions up to 5 years in the model. After 5 years people remained in the health state they were in at this time and moving to another health state was no longer allowed. The clinical experts confirmed that givosiran decreases the frequency of acute attacks in a few weeks. They expected that this effect would last for as long as a person has givosiran. The committee recalled that givosiran can also reduce chronic symptoms but this happened over several months (see section 4.5). The committee concluded that after 18 months people should remain in the health state they were in at that time. Only moving to the death state, in line with mortality in the general population, should be possible. After consultation, the company submitted updated data from the latest available ENVISION OLE data-cut. These data suggested that givosiran has a sustained effect on reducing acute attacks up to 36 months after the start of treatment. Based on this, the company extrapolated how people transition from 1 health state to another for the first 3 years in the model. After 3 years, people remained in the health state they were in at this time and moving to another health state was no longer allowed. The committee considered that this approach was consistent with the latest data and therefore acceptable for use in decision making.

Long-term effectiveness of prophylactic haem arginate

4.16 After consultation, the company submitted evidence for the effectiveness of the comparator prophylactic haem arginate. The ERG explained that the company's approach could best be described as an unanchored indirect comparison, in which plausible estimates for reduction in annualised attack rate (AAR) with prophylactic haem arginate were applied to the comparator arm. The ERG was confident that all relevant evidence was considered. The ERG agreed with the company's conclusion that a 'formal' network meta-analysis or indirect treatment comparison using for example, the Bucher method would not have been appropriate given the poor quality of available evidence. The committee concluded that the company's unanchored indirect comparison was acceptable

for use in decision making.

4.17 Modelling of long-term effectiveness of prophylactic haem arginate included 3 main components: rate of reduction in AAR, time taken to reach and sustain maximum effect and duration of treatment waning. Because of the limited evidence on the effectiveness of prophylactic haem arginate, there was uncertainty around the reduction of AAR, time to maximum sustained benefit and duration of treatment waning. The company therefore provided a 2-way threshold analysis to explore the effect of varying AAR reduction and time to maximum sustained benefit. A 3-way threshold analysis to explore the effect of varying AAR reduction, time to maximum sustained benefit and treatment waning was also provided.

4.18 The company used 2 sources, Marsden et al. (2015) and Neeleman et al. (2018), to inform the impact of prophylactic haem arginate on AAR reduction. Marsden et al. reported clinical benefit in 50% to 70% of people having prophylactic haem arginate. Neeleman et al. reported a 51.3% reduction in number of acute attacks in people having prophylactic haem arginate. The company interpreted the reduction in attacks reported in Neeleman et al. to be an AAR reduction that would be seen only among those people benefiting from prophylactic haem arginate. Also, the company explained that clinical experts had suggested it was likely that around 70% of people benefit from treatment with prophylactic haem arginate. Because of this, the company's base-case approach considered that 70% of people having prophylactic haem arginate have 51.3% AAR reduction. This resulted in a base-case AAR percentage reduction of 36%. The company considered this to be an overestimate of the true clinical benefit of prophylactic haem arginate because it relies solely on reduction in attack frequency without considering any other symptoms of AHP, such as chronic pain, neurological dysfunction, and psychiatric symptoms. The company also provided 3 additional scenarios of AAR reduction:

- 10% to model a minimum level of benefit, based on the company's assumption that clinicians would be unlikely to prescribe prophylactic haem arginate if the benefit were smaller than this
- 26% based on the assumption that 50% of people receiving prophylactic haem arginate benefit from a 51.3% AAR reduction

- 51% based on the assumption that all people having prophylactic harm arginate benefit from a 51.3% AAR reduction. The company suggested that this scenario implies effectiveness is approaching that of givosiran and therefore considered it clinically implausible.

  The ERG explained that they were not convinced by the company's interpretation of the Neeleman et al. data, which the company suggested showed that AAR reduction is conditional on treatment response. The ERG noted that AAR could be influenced by other unknown factors that do not relate to treatment response. Because of this, an absolute AAR reduction of 51% could be plausible. The committee noted there was uncertainty around the effectiveness of givosiran because of the lack of available data but agreed that AAR could be influenced by several factors. Therefore, the committee preferred to use an AAR reduction of 51% for decision making.

4.19 The company modelled time taken to reach and sustain maximum effect of prophylactic haem arginate as 5 years in its base case. The company explained that this was because of clinical feedback suggesting that benefits with prophylactic harm arginate would reach a maximum in the first year of treatment and then plateau out to approximately 5 years before starting to wane. The company also modelled 5 additional scenarios: 18 months, 3 years, 4 years, 6 years, and 7 years. Of these scenarios, the company considered only the scenarios ranging from 4 to 7 years as reasonable. This was based on available data from Neeleman et al. (which they suggested showed a median treatment duration of 4.2 years) and Marsden et al. (which reported a median observation period of prophylactic haem arginate of 6 years). Clinical experts explained that prophylactic haem arginate is generally effective for 1 year. After this, treatment-related adverse events begin to accumulate and eventually outweigh benefit but coming off treatment might precipitate further attacks. Based on this, the committee concluded that time to maximum and sustained benefit was likely to be 1 year. However, it noted that a 1-year scenario was not available for consideration. Because of this, the committee considered that it was most appropriate to consider a time to maximum and sustained benefit of 18 months in its decision making.

4.20 The committee understood that effectiveness of prophylactic haem arginate wanes over time. Clinical experts explained that this means attack rates and

chronic symptoms gradually increase over time. In the company base case, treatment waning (the period over which treatment effectiveness decreased) was assumed to be 23 years. This corresponded to the observation period over which Schmitt et al. (2018), a case series of 46 people with AHP, reported an increase in recurrent patients because of prophylactic haem arginate use. The company also modelled scenarios of no waning and waning periods of 3 years and 7 years. The clinical experts explained that many people remain on prophylactic haem arginate for 10 years or longer. However, this is generally because of difficulties associated with treatment stopping and because of patient reluctance to stop because of a lack of alternative treatments. Only minimal benefits remain after 3 to 4 years of prophylactic haem arginate. Based on this, the committee concluded that decision making should be based on a treatment waning duration of 3 years.

Stopping treatment

4.21 In ENVISION only 1 person stopped givosiran and this was because of adverse events. The clinical experts explained that in NHS clinical practice people might also have treatment breaks. For example, if the disease was asymptomatic (no attacks in 12 months) or there were few attacks (1 to 4 attacks in 12 months). They confirmed that there is little experience with treatment breaks; it is unclear when treatment would be stopped and how long breaks would last. Routine monitoring of symptoms and biochemistry would continue every 6 months during treatment breaks. The committee understood that clinicians would prefer to offer treatment for the minimum time and that people prefer a life without treatment. The committee concluded that because of the uncertainty about stopping and starting criteria for givosiran and their effect on outcomes it was not appropriate to include them in the model.

Time on treatment

4.22 The committee was aware that recurrent severe attacks most commonly appear in people between puberty and menopause. The clinical experts explained that attacks often stop at menopause so treatment is no longer needed. In the model, more people in the givosiran arm had no attacks at menopause and stopped

treatment than in the best supportive care arm. The committee noted that it should have been presented with an exploratory analysis estimating the effect of varying the numbers of women stopping treatment in both arms.

4.23 Because there are fewer men with AHP, there is less clinical experience and it is unclear whether attacks in men also stop or diminish with age. However, the clinical experts explained most people with AHP stop treatment approximately by the age of 50. It was highlighted that for some people this will be by the time of menopause onset, but the resolution of symptoms does not necessarily appear to be related to hormonal changes and may instead be simply age related. The committee concluded that few people might need lifelong treatment, but it was unclear how many this might be.

4.24 After consultation, the company submitted a scenario analysis in which 10% of the asymptomatic female cohort continued treatment beyond the menopause. This meant that 90% of this cohort stopped treatment at menopause. The clinical experts explained that 10% of the cohort continuing treatment after menopause was likely to be an overestimate. It was noted that in clinical practice, it is likely only 5% of people continue treatment beyond this point. Overall, the committee concluded that it was suitable for the model to consider men and 5% of the asymptomatic female cohort to continue treatment throughout the time horizon.

4.25 The company based its age of menopause onset on data from a Finnish cohort study by Greer et al. (2003). A scenario analysis based on data from the UK Women's Cohort study was also presented. The ERG considered the UK Women's Cohort study to be more generalisable to NHS clinical practice. Also, the ERG explained that while the mean age of menopause onset included within the model (50.5 years) is similar between sources, there is considerable difference in distributions between both data sources. The UK Women's Cohort study uses a normal distribution, but the Greer et al. study has an irregular distribution based on data. Because of this, the probability of menopause onset in each cycle of the model might be different using each data source. The committee understood that the choice of data source for menopause onset had minimal effect on cost-effectiveness results and therefore concluded that both the ERG and company approach are suitable for use in decision making.

4.26 Because of the short follow-up time in ENVISION (up to 18 months) there is only

limited clinical data on how long people stay on treatment. So, fitting an appropriate parametric model was challenging. Based on clinical plausibility, the company fitted a log-logistic model to the Kaplan–Meier curve based on observed data from ENVISION and ENVISION OLE. Because cost-effectiveness results change substantially with time-on-treatment estimates, the ERG explored alternative methods. This included a piecewise approach using the Kaplan–Meier curve based on observed data followed by the log-normal model. The committee recalled that most people stop treatment at menopause (see section 4.24). It noted that the log-logistic approach provided a more plausible estimate of the proportion of people remaining on treatment at the end of the time horizon, compared with the piecewise approach. The committee concluded that time-on-treatment estimates were very uncertain but accepted the company's approach using a log-logistic model.

Quality-of-life data used in the model

4.27 To look at the effect on quality of life, the model used a 2-step approach to include the chronic symptoms of the disease and the acute attacks. EQ-5D-5L data collected in ENVISION (see section 4.11) was not used in the model. Instead, the company used utility values for each chronic symptom from the literature. It used data from the EXPLORE study, a natural history study of people with AHP, for utilities associated with acute attacks. The clinical experts explained that it is challenging to use trial data to determine the quality of life for people who have acute attacks. They suggested that ENVISION utilities could be used for the chronic symptoms. The committee cautioned that these did not appear plausible because they suggested higher quality of life in more severe health states. It agreed that the company's approach of summing the effect of single chronic symptoms was flawed. It preferred the ERG's approach of using utilities from relapsing–remitting multiple sclerosis as the best available proxy for the chronic symptoms. After consultation, the company maintained its original approach. The company suggested that using relapsing–remitting multiple sclerosis utilities is inappropriate because of differences in disease processes and resulting symptoms compared with AHP. The committee agreed that there are some differences in chronic symptoms between relapsing–remitting multiple sclerosis and AHP, however considered the severity of impact on quality of life to be similar. The committee had concerns that the company's approach may have

been associated with double counting of some chronic symptoms (for example, pain). Overall, the committee concluded that using utilities from relapsing–remitting multiple sclerosis to model the chronic symptoms and from EXPLORE to model the acute attacks was reasonable.

Number of people with chronic symptoms

4.28 The ERG challenged the sources of treatment costs for chronic symptoms and how costs were included in the model. The committee agreed that a micro-costing approach should only be used when each symptom needed separate resources. Also, costs should come from the most recent publications, the Personal and Social Services Research Unit or health resource groups. The clinical and patient experts explained that people with chronic pain often use opioids and that opioid dependency was an issue for some people. The committee agreed to include costs of opioid dependency in the model. It concluded that including the costs of treating chronic symptoms added uncertainty and this should be further explored using alternative cost sources. After consultation, the costs of treating chronic symptoms was updated based on a targeted literature search done in June 2021. The committee considered the new costs to be appropriate.

Age at model entry

4.29 Clinical experts advised that people are diagnosed with AHP in their 20s or 30s. Often people in their 30s start treatment with haem arginate to prevent recurrent acute attacks. The median age of people entering the model in the company's base case was 42 years. Because most people in the givosiran arm stopped treatment at menopause age at model entry, this had a substantial effect on the cost-effectiveness results. The clinical experts at the first committee meeting confirmed that the median age of people who have prophylactic treatment for recurrent severe attacks and would be eligible for givosiran in the NHS is early 40s. However, if givosiran was recommended, anyone newly diagnosed with recurrent severe attacks would become eligible at diagnosis so people starting treatment would be younger. The committee concluded that the starting age for treatment is an important model driver and that an analysis of the effect of

varying starting age should be provided using information from people with AHP currently having treatment in the NHS. After consultation, the company provided a scenario analysis with the starting age of givosiran set at 37 years. The company explained that this is similar but younger than the lower bound of the 95% confidence interval for age at baseline in the ENVISION EU population (37.9 years). Also, it is younger than the median age at baseline in the EXPLORE natural history study (38 years). The company suggested that the similarity of evidence from the ENVISION and EXPLORE studies supports 37 years being the lowest plausible starting age. The clinical experts considered 37 years to be an accurate reflection of starting age in clinical practice. The committee concluded a starting age of 37 years was suitable for use in decision making.

Cost-effectiveness results

4.30 The company and NHS England have agreed a confidential commercial discount. The company considers all plausible incremental cost-effectiveness ratio (ICER) results of the economic analysis incorporating this discount commercial in confidence, so the exact ICERs cannot be reported.

4.31 The committee considered the following assumptions to be the most appropriate for decision making:

- allowing people to move between health states in the first 36 months, after which they remain in the same health state in the givosiran arm (see section 4.15)
- long-term effectiveness of prophylactic haem arginate modelled as:
  - 51% reduction in AAR (see section 4.18)
  - 18 months duration to reach and sustain maximum effect (see section 4.19)
  - 3 years duration of treatment waning (see section 4.20)
- continuing treatment throughout the time horizon for men and 5% of the asymptomatic female cohort after onset of menopause (see section 4.24)

- using the log-logistic model to extrapolate time on treatment (see section 4.26)
- using utilities from relapsing–remitting multiple sclerosis (see section 4.27)
- including the updated costs associated with chronic symptoms (see section 4.28)
- including the costs of opioid dependency (see section 4.28)
- using a treatment starting age of 37 within modelling (see section 4.29).

The committee recalled that both the company's and the ERG's data source for age of menopause onset were suitable for use in decision making and had limited effect on cost-effectiveness results (see section 4.25).

4.32 Overall, the committee noted that applying all their preferred assumptions resulted in an ICER over £100,000 per quality-adjusted life year (QALY) gained and an incremental undiscounted QALY of 18.6.

Applying QALY weighing

4.33 The interim process and methods of the highly specialised technologies programme 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 size of the incremental therapeutic improvement. This is revealed through the number of additional unadjusted 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 unadjusted QALYs. The committee discussed the QALY gains associated with givosiran compared with prophylactic haem arginate. It noted that, using the committee's preferred assumptions (see section 4.31), the undiscounted QALY gain was 18.6. The committee therefore concluded the givosiran met the criteria for a QALY weight of 1.8. The committee was satisfied that givosiran would offer significant QALY gains, and therefore applied this weighting in its consideration of

its value for money.

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

4.34 The committee discussed the effects of givosiran beyond its direct health benefits and the evidence of the patient experts. The patient and clinical experts explained that all aspects of people's lives, and those of their families and carers, are affected by the condition. Most people with AHP cannot live independent lives and rely on family and carers at least some of the time. If people have to give up work they will be worse off financially. The committee agreed that the carer disutilities used in the model were higher than expected for a disease that usually starts in adults. The patient experts explained that givosiran had completely changed their experience of living with AHP. Recurrent attacks needing hospitalisation and chronic pain decreased substantially, so they seldom needed painkillers. The clinical experts explained that there is high unmet need within people with AHP. It was noted that current treatment is limited to prophylactic haem arginate. This treatment is associated with low effectiveness and frequent adverse events. The committee also noted comments from patient organisations received during consultation, which highlighted that using givosiran could reduce the need for liver transplantation. The committee recalled that liver transplantation is associated with important lifelong consequences and health risks. Overall, the committee concluded that givosiran may affect people beyond its direct health benefits, but it noted that the full effect of these benefits had not been fully quantified. The committee considered these benefits in its decision making.

Other factors

4.35 The committee noted that AHP is more common in women than men. However, it concluded that its recommendation applies equally, regardless of gender, so this difference is not in itself an equality issue.

4.36 The committee discussed the innovative nature of givosiran, noting that the company and clinical experts considered the drug's mechanism of action to be a step change in managing AHP. The patient experts explained that having givosiran available would change the course of their condition. The committee took this into account in its decision making.

Conclusion

4.37 The committee concluded that AHP is a rare, serious and potentially life-threatening condition that can affect the lives of patients, their families and carers. It recognised that there is an unmet need for effective and safe treatment options for preventing recurrent severe attacks. It agreed that givosiran provided substantial clinical benefit compared with best supportive care. Treatment with prophylactic haem arginate is established clinical practice in the NHS because it provides some clinical benefit, however treatment effect wanes over time. Also, treatment with prophylactic haem arginate is associated with frequent adverse events. The committee recognised that there was no clinical data directly comparing givosiran with prophylactic haem arginate. However, it considered that available evidence combined with clinical and patient expert input suggested that givosiran would be able to reduce the frequency of acute attacks, improve chronic symptoms and improve quality of life for people with AHP. The committee considered the company's base case, 2-way and 3-way threshold analyses, and ERG scenario analyses. It noted that givosiran met the criteria for a QALY weighting to be applied. It also acknowledged the uncertainties of the treatment duration of givosiran and the effectiveness of prophylactic haem arginate and considered other benefits of givosiran that were not captured in the analysis. The committee concluded that the most plausible ICER for givosiran in people with AHP aged 12 or older with clinically confirmed severe recurrent acute attacks (4 or more attacks within 12 months), is likely to be within the range NICE normally considers an effective use of NHS resources for highly specialised technologies when the QALY weighting, and the company's confidential discount are applied.

5 Implementation

5.1 Section 8(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

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 AHP and the doctor responsible for their care thinks that givosiran is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Evaluation committee members and NICE project team

Evaluation committee members

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

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

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

NICE project team

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

Verena Wolfram and Fatima Chunara
Technical leads

Sally Doss and Victoria Kelly
Technical advisers

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