NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

Pegzilarginase for treating arginase-1 deficiency in people 2 years and over

1 Recommendation

1.1 Pegzilarginase can be used, within its marketing authorisation, as an option to treat arginase-1 deficiency (also called hyperargininaemia) in people 2 years and over.

What this means in practice

Pegzilarginase must be funded in the NHS in England for the condition and population in the recommendations, if it is considered the most suitable treatment option. Pegzilarginase must be funded in England within 90 days of final publication of this guidance.

There is enough evidence to show that pegzilarginase provides benefits and value for money, so it can be used routinely across the NHS in this population.

Why the committee made this recommendation

Usual treatment for arginase-1 deficiency includes dietary protein restrictions, essential amino acid supplementation and ammonia-lowering drugs. Pegzilarginase is the first treatment that specifically treats arginase-1 deficiency.

Clinical trial evidence shows that pegzilarginase plus usual treatment reduces levels of arginine in the blood compared with placebo plus usual treatment. Evidence also suggests improvements in mobility and mental processing, but this is uncertain because the studies were small and short. So, it is unclear how large these benefits are or how long these improvements will last.

Despite the uncertainties in the clinical and economic evidence, the most likely cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources for highly specialised technologies. So, pegzilarginase can be used.

2 Information about pegzilarginase

Marketing authorisation indication

2.1 Pegzilarginase (Loargys, Immedica) is indicated 'for the treatment of arginase-1 deficiency (ARG1-D), also known as hyperargininemia, in adults, adolescents and children aged 2 years and older'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for pegzilarginase.

Price

2.3 The list price for pegzilarginase is £4,690.00 per 2-mg vial (excluding VAT, company submission).

2.4 The company has a commercial arrangement. This makes pegzilarginase available to the NHS with a discount. The size of the discount is commercial in confidence.

Sustainability

2.5 Information on the Carbon Reduction Plan for UK carbon emissions for Immedica will be included here when guidance is published.

3 Committee discussion

The evaluation committee considered evidence submitted by Immedica, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Arginase-1 deficiency

3.1 Arginase-1 deficiency is an ultra-rare inherited progressive metabolic condition characterised by increased levels of arginine and its metabolites. It is caused by a deficiency of the arginase-1 enzyme, which is active in the urea cycle. Arginase-1 deficiency can have substantial and debilitating complications, including spastic paraparesis, progressive neurological and motor deterioration affecting mobility, growth and developmental delays, cognitive delays, and seizures. The condition has a substantial impact on health, quality of life and survival. The patient and carer submissions highlighted that arginase-1 deficiency has a profound impact on people with the condition and their carers, including on physical and mental health, and social and work life. They explained that the need for regular medical appointments with various specialists and the high frequency of hospitalisations, including for life-threatening emergencies, can be extremely burdensome. The patient experts also highlighted that delayed diagnosis is an issue and diagnosis is sometimes made at more severe stages of disease. The clinical expert submissions highlighted that some people with the condition may need a liver transplant. The committee concluded that arginase-1 deficiency is a debilitating condition with multiple comorbidities, poor survival, and a substantial impact on quality of life for people with the condition and their carers.

Clinical management

Treatment options

3.2 Treatments for arginase-1 deficiency aim to reduce plasma arginine levels, delay disease progression and improve quality of life. There are no available disease-modifying treatments for arginase-1 deficiency. Current treatment involves individualised disease management, including dietary protein restrictions, essential amino acid supplementation and ammonia-lowering drugs. The company proposes pegzilarginase as a treatment option for the long-term management of arginase-1 deficiency alongside individualised disease management. The clinical experts highlighted that

the condition progresses, with physical and cognitive deterioration, despite current treatment. They also noted that plasma arginine levels are almost never reduced to target levels despite extremely restrictive dietary management that is difficult to adhere to. The patient experts explained that current clinical management can be extremely burdensome. Both the clinical and patient experts explained the unmet need for a disease-modifying treatment for arginase-1 deficiency. The clinical and patient experts highlighted that pegzilarginase is a step-change treatment that can reduce plasma arginine to target levels, stop disease progression and improve clinical outcomes. They further highlighted the additional benefits of pegzilarginase treatment, including reducing the need for an extremely restrictive diet and stopping ammonia-lowering drugs. The committee noted that there is an unmet need for a disease-modifying treatment for arginase-1 deficiency. It concluded that pegzilarginase can potentially fulfil this unmet need.

Clinical effectiveness

Data sources

3.3 The clinical-effectiveness evidence for pegzilarginase came from 3 multicentre trials that included people with arginase-1 deficiency aged 2 years and over, some of whom were from the UK:

- PEACE was a phase 3, randomised, double-blind, placebo-controlled trial followed by an open-label, long-term extension. A total of 32 people were randomised to either pegzilarginase plus individualised disease management (from now, pegzilarginase) or placebo plus individualised disease management (from now, placebo) for 24 weeks. People in the placebo arm then switched to pegzilarginase for an 8-week blinded period. Everyone remained on pegzilarginase for up to 150 weeks of long-term extension. The primary outcome was change in plasma arginine level. Secondary outcomes included:
  - the 2-minute walk test
  - Gross Motor Function Measure-88 Part E (GMFM-E)
  - GMFM-88 Part D (GMFM-D)

  - Vinelands Adaptive Behaviour Scale-2 (VABS-2)
  - the Weschler Intelligence Scale
  - levels of ornithine and guanidino compounds
  - adverse events
  - health-related quality of life.
- Study 101A and Study 102A evaluated the long-term safety and tolerability of pegzilarginase. Study 101A was a 20-week phase 1 and 2, single-arm, open-label, 2-part dose-finding study of pegzilarginase (n=16). Study 102A (n=14) was a single-arm, open-label, long-term extension (up to 3 years) of Study 101A. The primary outcome in Study 101A and Study 102A was adverse events. Secondary outcomes included:
  - plasma arginine level
  - 6-minute walk test
  - GMFM-E
  - GMFM-D
  - health-related quality of life.

The committee noted the small number of people in the trials. It was aware that newborn screening for the condition is not routine practice in the NHS. But, in some trial locations, people may be identified by newborn screening.

Clinical outcomes

3.4 The company presented pooled results of PEACE and Study 102A for plasma arginine levels and mobility outcomes at week 24 as follows:

- Pegzilarginase showed a statistically significant reduction (77.9%) in mean plasma arginine level compared with placebo.
- For the 2-minute and 6-minute walk tests, the percentage change from baseline was used instead of the observed walking distance to analyse the data in the same scale. At week 24, the mean changes from baseline in the timed walk test were 9.2% for the pegzilarginase arm and 4.1% for the placebo arm. The least squares mean difference

between treatment arms was 6.0% and not statistically significant (95% confidence interval [CI] -19.6% to 31.6%; p=0.6409).

- The least squares estimate of the mean change from baseline in GMFM-E score at week 24 for the pegzilarginase arm was 3.5 (95% CI 1.2 to 5.8) and for the placebo arm was -1.1 (95% CI -5.3 to 3.2). The least squares mean difference between treatment arms was 4.6 and not statistically significant (p=0.0703).
- The least squares estimate of the mean change from baseline in GMFM-D score for the pegzilarginase arm was 2.2 (95% CI 1.2 to 3.2) and for the placebo arm was 0.0 (95% CI: -2.0 to 1.9). The least squares mean difference between treatment arms was 2.2 (p=0.0504).

The EAG highlighted that pegzilarginase appeared to have a large effect on plasma arginine levels within the first 24 weeks. But clinical advice to the EAG noted that plasma arginine levels do not have a consistent relationship with disease severity. The EAG highlighted that mobility, mental processing and quality-of-life outcomes were uncertain because the results lack clinical and statistical significance. It also highlighted that long-term outcomes were uncertain because of the lack of a comparator arm in the long-term extension of PEACE and Study 102A, and presence of underpowering from small numbers of participants (see section 3.3). But the EAG explained about the plausible ceiling effect for mobility and spasticity outcomes. The clinical experts highlighted that it is not possible to reduce plasma arginine to target levels with current clinical management in the NHS for arginase-1 deficiency. This is, in part, because of continuous arginine production in the blood. The clinical experts also explained that plasma arginine level is an appropriate surrogate outcome despite not being the only marker for disease severity. The committee noted that some other outcomes, such as the 2-minute walk test, may not be appropriate to reflect how treatment is modelled. The committee also noted the absence of survival data in the company's submission. The clinical experts explained it is plausible that pegzilarginase would

extend survival, but this is uncertain. The committee concluded that pegzilarginase reduces plasma arginine levels, an important outcome for arginase-1 deficiency. But it decided that life extension with pegzilarginase was uncertain, given the lack of longer-term data.

Economic model

Company's modelling approach and starting ages

3.5 The company presented a cohort-level Markov model with a lifetime horizon for people with arginase-1 deficiency having either pegzilarginase plus individualised disease management or individualised disease management alone. People in the model progressed through different health states. These were defined by the level of mobility (expressed as Gross Motor Function Classification System [GMFCS] scores) and death. In any GMFCS health state, people could have hyperammonaemic crises needing hospitalisation or emergency department management. Hyperammonaemic crises were associated with increased healthcare costs and worsening of health, including the possibility of death. Deaths unrelated to arginase-1 deficiency could occur at any time in the model. Cognitive ability, categorised as mild to normal, moderate, or severe impairment, was modelled separately to GMFCS health states. The model also considered the burden on carers associated with each GMFCS health state and the potential benefit of a less-restricted diet associated with pegzilarginase treatment. The committee requested additional analyses after the first committee meeting. The company included results of a Delphi panel involving clinical expert consensus on mean age in each health state. These were:

- GMFCS-1: 11 years
- GMFCS-2: 12 years
- GMFCS-3: 16 years
- GMFCS-4: 25 years
- GMFCS-5: 15 years.

The company noted that the mean starting age in the GMFCS-5 health

state was lower than in the GMFCS-4 health state. This was because of people who transitioned from the GMFCS-2 and -3 health states after severe hyperammonaemic crisis. The company used a mean age of 13 years for everyone in the economic model. The NICE technical team noted that the model starting age appeared young, given that a high proportion of people with arginase-1 deficiency in the NHS population are adults. A survey of 12 healthcare professionals (7 from England) submitted by Metabolic UK and draft guidance consultation responses from clinical experts reported that, out of 21 people in England, 12 were adults. The committee concluded that a model starting age of 13 years was acceptable for decision making. But it thought that it may represent a younger age than that seen in the current NHS England population.

Starting distributions by GMFCS health states

3.6 In the company's base-case model, pooled data (n=64) from PEACE, Study 101A, Study 102A and a European burden of illness survey (n=16) was used to inform the starting distributions of people across GMFCS health states. The company highlighted that this approach used more data, was likely to be more representative of NHS clinical practice and included all GMFCS health states at baseline. Clinical advice to the EAG suggested that the starting distributions in the NHS in England may be more like those in the European burden of illness survey. This is because PEACE, Study 101A and Study 102A may have underrepresented people with more severe disease. The EAG provided a scenario analysis using data from the European burden of illness survey to inform the starting distribution of people in each GMFCS health state. The clinical experts stated that most people in the more severe GMFCS-4 and GMFCS-5 health states are likely to be adults. The clinical experts also explained that if there were improvements in practice that led to the earlier diagnosis of arginase-1 deficiency, there would be larger distributions in less severe GMFCS health states. The patient experts highlighted that people with delayed diagnosis could be expected to be in more severe GMFCS health states. The company noted that currently in England about 50% of people

with the condition are adults. At the first committee meeting, the committee noted that the starting distributions from the European burden of illness survey were more representative of NHS clinical practice than the company's approach. It concluded that the starting distributions of people across each GMFCS health state informed by the European burden of illness survey was the most appropriate option. The committee requested further details on the current population with the condition in the NHS in England. This was because starting distributions have the potential to substantially impact cost-effectiveness estimates.

At the second committee meeting, the company maintained that using pooled data from PEACE, Study 101A, Study 102A and the European burden of illness survey was the most appropriate approach to estimate distributions across health states. It stated that results from the Delphi panel showed expert consensus that the company's base case reflects the population that would likely have pegzilarginase if recommended by NICE. In their responses to draft guidance consultation, clinical experts and Metabolic UK provided information on the distribution of people with the condition in England across GMFCS health states (n=21). The NICE technical team noted that this stakeholder information suggested a higher proportion of people in the NHS in a more severe GMFCS state than what was represented in the company's modelling or the burden of illness survey. Also, the committee noted that a higher proportion of people were in the GMFCS-3 health state in the healthcare professional survey results (around 14%) than in the company base case (around 3%) or in the European burden of illness survey (0%). The clinical experts also stated that the decision to treat arginase-1 deficiency is individual to each person with the condition. They noted that there would be some people in the prevalent population who would not have pegzilarginase, particularly some people in the GMFCS-5 health state. The committee acknowledged the prevalent population was the appropriate population to consider. But it noted that, based on the opinion of clinical experts, pegzilarginase may not be offered to everyone with arginase-1 deficiency. The committee concluded that applying a distribution based on the European burden of

illness survey was appropriate. But it decided that starting with no people in the GMFCS--3 health state was implausible. It also thought that the distribution should be adjusted to assume that the same proportion of people would be in the GMFCS-2 and -3 health states (15.625%). This was because it would better represent the prevalent population in the NHS in England, as reported by the healthcare professional survey and clinical expert input.

Disease progression

Transition probabilities for pegzilarginase

3.7 In the company's base case, initial disease progression was modelled by estimating transition probabilities between GMFCS health states using the observed counts of GMFCS changes between visits in PEACE. For pegzilarginase, a time-invariant transition matrix was estimated based on an average of 96 weeks of data, which was assumed to apply for 3 years (157 weeks). After 3 years, it was assumed that people having pegzilarginase stayed in the same GMFCS health state for the remainder of the model time horizon. The company submission highlighted that the combined GMFM-D and GMFM-E scores (GMFM-DE) were still improving for some people up to 4 years after starting pegzilarginase. It noted that controlled plasma arginine levels result in controlled underlying disease pathogenesis and that people cannot become resistant to pegzilarginase. Clinical advice to the EAG thought it plausible that people on pegzilarginase would remain in the same GMFCS health state after 3 years. But the EAG highlighted that this assumption was very uncertain because it solely relied on clinical expert opinion. The EAG explained that PEACE only reported data on mobility outcomes for a short period of time. The clinical experts thought that the company's assumption that people on pegzilarginase would remain in the same GMFCS health state after 3 years was plausible. But they noted that it was not possible to be certain that disease progression would not occur in the future. They explained that, although disease stabilisation is hard to achieve, arginase-1 deficiency is a slow, progressive disease. So, it is possible for people to

remain in the same GMFCS health state with some disease progression, particularly in more severe GMFCS health states. But the clinical experts thought that this may be difficult to capture in the economic model. The company further highlighted that, at 3 years, about 90% of people remained in the same GMFCS health state in PEACE and others improved to less severe health states. The clinical experts explained that, even in more severe health states, there are likely to be small improvements with pegzilarginase that make a meaningful difference to the quality of life of people with arginase-1 deficiency. This would not be seen for people having standard care. The committee noted that the assumptions around long-term efficacy had a very large impact on the cost-effectiveness estimates. The committee thought that the company's assumption that people in the pegzilarginase arm remained in the same GMFCS health state after 3 years was very uncertain. But, in the absence of longer-term clinical trial evidence, it relied on clinical expert opinion that the company's assumption was plausible. The committee concluded that assuming people in the pegzilarginase arm remained in the same GMFCS health state after 3 years was appropriate for decision making. But it thought that this was associated with very high levels of uncertainty.

Transition probabilities for standard care arm

3.8 For the standard care arm, a time-invariant transition matrix was estimated based on 24 weeks of data. Long-term transition probabilities beyond 24 weeks were estimated using the relationship between GMFCS health state and GMFM-DE score. The average time taken to move through GMFCS health states was then estimated using the relationship between GMFM-DE score and patient age. A reduction in GMFM-DE score of 1.45 per year was used based on the midpoint of a 95% CI of 0.23 to 2.66. Constant transition probabilities were then generated using the inverse of mean time in a health state, converted from annual to cycle-specific transition probabilities. The EAG noted that the inverse of time spent in a GMFCS health state should have been converted to a probability and applied this in its base case. During the committee meeting, the company agreed with the EAG's base-case approach. The

EAG also highlighted that the company's assumed starting GMFM-DE score in the GMFCS-1 health state was unlikely. This was because it suggests that people can have arginase-1 deficiency without deterioration in GMFM-DE score. Instead, the EAG used the mean GMFM-DE score from PEACE, Study 101A and Study 102A for people starting in the GMFCS-1 health state in its base case. The EAG also used the upper limit of the 95% CI (2.66) of reduction in GMFM-DE score per year in its base case. The committee noted that the EAG's base-case approach reduced the mean time of moving from GMFCS-1 to GMFCS-5 to a value that was more aligned with clinical estimates (the exact values are considered confidential by the company and cannot be reported here). At the first committee meeting, the committee decided that the following assumptions to model transition probabilities in the standard care arm were appropriate:

- mean of PEACE, Study 101A and Study 102A used as the starting GMFM-DE score for people in the GMFCS-1 health state
- a reduction in GMFM-DE score of 2.66 per year
- inverse of time spent in a GMFCS health state converted to a probability.

For the second committee meeting, the company updated the annual reduction in GMFM-DE score to 3.17. This was higher than the 2.66 reduction preferred by the committee in the first meeting. It also redefined GMFM-DE cut-offs for GMFCS health states. This was so the average age for that health state occurred halfway through the time in each respective GMFCS health state. The clinical experts suggested that the times spent in each health state were reasonable. But progression through the states in the EAG's original base case, used at the first committee meeting, were longer than they would have expected. The EAG noted that the company did not provide rationale for using a GMFM-DE reduction of 3.17 instead of the committee-preferred reduction of 2.66. The EAG stated that the new approach relied on several assumptions derived from the Delphi panel, which

added uncertainty. It also stated that there was no justification to determine that this new approach was superior to the EAG's original base case. The EAG preferred to use the difference in average ages from the Delphi panel rather than using GMFM-DE score ranges. This resulted in a slower progression through the GMFCS-2 and -3 health states, but these figures were closer to the company's base case. The committee acknowledged the clinical experts' comments that the company's estimated time in each health state better reflected NHS clinical practice than did the EAG's original base case. It concluded that the updated EAG analysis using average age to determine time in state was most appropriate for decision making.

Transition from GMFCS-2 and -3 to GMFCS-5 after hyperammonaemic crisis

3.9 In its original model, the company assumed people would progress through each GMFCS state sequentially. For the second committee meeting, the company's revised model assumed that, each year, a small proportion (5%) of people in the GMFCS-2 and -3 states would progress to GMFCS-5 after a severe hyperammonaemic crisis. The company stated that 5% was a conservative approach because the Delphi panel consensus was that 5% to 10% of people with the condition would progress. The EAG highlighted that this assumption was only applied to the standard care arm and not the pegzilarginase arm. It also noted that clinical input said such a transition would usually only happen in early childhood. But the company had modelled it to occur at all ages. The EAG provided analyses that assumed that the transition from GMFCS-2 and -3 to GMFCS-5:

- did not happen in people 16 years and over
- could also occur in the pegzilarginase arm.

The clinical experts stated that severe hyperammonaemic crises were rare events for adults. Stakeholder responses to the draft guidance consultation indicated that some hyperammonaemic crises still occur

while on pegzilarginase. But the clinical experts highlighted that the ammonia levels were not severely increased in these events. The committee concluded that the EAG's analysis was appropriate for decision making.

Life expectancy

Original company base case

3.10 In its base case, the company adjusted the economic model so that nearly everyone in the standard care arm died by age 35 years. This included death associated with hyperammonaemic crisis. To apply this adjustment the company made the following assumptions:

- It used the standardised mortality rates from NICE's highly specialised technology guidance on atidarsagene autotemcel for metachromatic leukodystrophy (from now, HST18) compared with an age- and sex-matched population to capture the impact of neurodisability on mortality. This was based on clinical advice that metachromatic leukodystrophy is a similar condition to arginase-1 deficiency. These rates were generalisable for people with arginase-1 deficiency having pegzilarginase, after removing the toxicity associated with the treatment for metachromatic leukodystrophy (atidarsagene autotemcel).
- It obtained standardised mortality rates by applying a multiplier to the pegzilarginase arm.

In its adjustment, the company estimated a standardised mortality rate for the standard care arm that was 800 times greater than that for the pegzilarginase arm. This resulted in 0.0008% of people alive at age 35 years in the standard care arm. Clinical advice to the EAG suggested that it was unlikely that nearly everyone would die by age 35 years. The EAG noted that 1 participant in the European burden of illness survey was aged 49 years. To address the uncertainty in the standardised mortality rate for the pegzilarginase arm and the company's assumption that nearly everyone in the standard care arm died by age 35 years, the

EAG provided the following scenario analyses:

- It assumed that the standardised mortality rate for the pegzilarginase arm was twice that assumed in the company's base case. This resulted in a standardised mortality rate for the standard care arm that was 500 times greater than that for the pegzilarginase arm.
- It assumed that nearly everyone died before age 50 years in the standard care arm and that everyone was 4 years old at the start of the model. This took into account that some people may have died between 4 years and the mean age used in the base-case model. This resulted in a standardised mortality rate of 200, resulting in 0.0007% of people being alive at age 50 years.
- It assumed a calibration based on the model starting age that resulted in a standardised mortality rate in which 0.0033% of people were alive at age 35 years (the starting age and standardised mortality rate values are considered confidential by the company and cannot be reported here).

One clinical expert highlighted that some people would be expected to live beyond 35 years with current standard care, even without pegzilarginase. They explained that clinical management for arginase-1 deficiency has improved. The committee noted the lack of survival data from the clinical trials used to inform mortality in the economic model. It questioned the company's approach of using standardised mortality rates to model mortality. It also questioned whether the EAG's scenario analysis that doubled mortality rate for the pegzilarginase arm was informative. The EAG explained that doubling the standardised mortality rates did not have much impact on estimated mortality. This was because the standardised mortality rates were assumed to be low and applied to low risks of death (general population risks). It suggested that a scenario with higher standardised mortality rates may be informative. The company highlighted that no Kaplan–Meier survival data was available from clinical trials. The company also explained that, although survival curves could be generated

for GMFCS health states, these health states are also affected by neurological outcomes. So, standardised mortality rate was thought to be the best approach to simulate mortality in the economic model. The EAG highlighted that hyperammonaemic crises have a larger impact on mortality than the standardised mortality rates used in the model. The committee also questioned why the estimated life years gained with pegzilarginase were consistent across all GMFCS health states, as shown in the NICE technical team's scenario analyses by GMFCS subgroups. The EAG explained that these analyses were not recalibrated. It added that mortality in the model was driven by hyperammonaemic crises, which are independent of GMFCS health states. The committee thought that there was considerable uncertainty in how mortality was modelled in the company's base-case approach. It recalled clinical expert advice that some people would be expected to live longer than 35 years with improved clinical management for arginase-1 deficiency. It also recalled that hyperammonaemic crises drove mortality in the economic model. The committee concluded that the standardised mortality rate for the pegzilarginase arm in the company's base case may be appropriate. But it thought that this was uncertain because of the low standardised mortality rates and similar results by GMFCS subgroup. After the first committee meeting, the committee requested further analyses around mortality in the model. This included a request for further scenario analyses around standardised mortality rates and life years gained by GMFCS health state. It also concluded that the scenario analysis in which nearly everyone in the standard care arm died at age 50 years was appropriate.

Updated company base case

3.11 For the second committee meeting, the company did not apply the committee preferences from the first meeting. Instead, it provided recalibrated standardised mortality rates based on input from the Delphi panel. The company stated that the Delphi panel reached consensus that diagnosis occurred at about 5.1 years and that 90% of people with arginase-1 deficiency having standard care died by age 32 years. The Delphi panel also reached consensus on a mortality distribution by

GMFCS health state for people having individualised treatment management. Based on this feedback, the company updated its base case to include:

- assigning everyone in the model to GMFCS-1 with a starting age of 5.1 years
- applying a multiplication factor so that, at age 50 years, 99% of people having standard care had died
- having individual multipliers for each health state based on the distribution of mortality from the Delphi panel, with a further adjustment so that GMFCS-5 had 90% mortality by 32 years.

The company also did not provide further supportive evidence, as requested by the committee, that metachromatic leukodystrophy (HST18) was an appropriate proxy condition. Stakeholder comments from clinical experts and Metabolic UK stated that 8 healthcare professionals in a survey responded to a question around life expectancy for people who had pegzilarginase. Seven of them (87.5%) stated that they expected pegzilarginase to improve life expectancy. Five healthcare professionals also stated that they thought this improvement could extend from 'many years' to 'normal life expectancy'. The stakeholder responses also stated that no other condition could exactly align with arginase-1 deficiency, but that metachromatic leukodystrophy could be a valid proxy. But it did not cover risks of hyperammonaemia. NICE's technical team noted that HST18 evaluated a gene therapy that works differently to pegzilarginase.

The EAG stated that the company's new approach had many limitations. Firstly, the Delphi panel conclusions and estimates were uncertain because the company assumed that a 'somewhat agree' response meant consensus. Secondly, the company's standardised mortality ratio for GMFCS-5 was markedly lower than the standardised mortality ratio for GMFCS-4. This raised concerns about the face

validity of the approach. Thirdly, while the company said the approach in the pegzilarginase arm was conservative, this cannot be confirmed because of the uncertainty in the long-term overall survival. NICE's technical team noted that using HST18 for all standardised mortality ratios in the pegzilarginase arm, as in the company's original base case, increased the cost-effectiveness estimates. The EAG stated that increasing the standardised mortality ratio in more severe health states was likely to benefit pegzilarginase. NICE's technical team noted that the standardised mortality rates in the GMFCS-1 and -2 states for the pegzilarginase arm were markedly low in both the company's (1.16) and EAG's (1.32) analyses. Also, because most people in the pegzilarginase arm remained in these states, these results were almost suggestive of a cure. The team also noted that the company previously stated that arginase-1 deficiency would have some impact on health and mortality before people have pegzilarginase. The committee noted that a low standardised mortality rate in the GMFCS-1 health state for the pegzilarginase arm may have been plausible. But it noted that being in this health state does not equal full health. It said that the low standardised mortality rate for the GMFCS-2 health state was less certain. The committee noted that this issue affected the quality-adjusted life years (QALY) weighting (see section 3.20). It noted that the standardised mortality ratios were still highly uncertain and may have underestimated the cost-effectiveness results. It also noted that using the standardised mortality ratios from HST18, as in the company's original base case, significantly increased the cost-effectiveness estimates. The committee concluded that the standardised mortality ratios for pegzilarginase in the EAG's analysis were the most plausible. But it preferred to amend the GMFCS-2 standardised mortality rate to be 25% of the rate seen in the standard care group. This was to reflect the potential impact of a hyperammonaemic crisis.

Distribution of peak ammonia levels during hyperammonaemic crisis

3.12 In the company's base-case model, a proportion of hyperammonaemic crises were assumed to result in death. To estimate the risk of death because of a hyperammonaemic crisis, the company used data from the Urea Cycle Disorders Consortium registry. This provided estimates of mortality based on age (between 2 and 12 years, and over 12 years) and 4 peak ammonia categories (up to 200 micromoles per litre; 201 to 500 micromoles per litre; 501 to 1,000 micromoles per litre; and 1,001 micromoles per litre and above). For the distribution of peak ammonia in the standard care arm, data was pooled from Bin Sawad et al. (2022), the Urea Cycle Disorders Consortium registry and the placebo arm of PEACE (the number of episodes is considered confidential by the company and cannot be reported here). For the pegzilarginase arm, the company considered all hyperammonaemic crisis episodes in people who had treatment for at least 24 weeks. The EAG highlighted that there was considerable uncertainty about the peak ammonia levels during a hyperammonaemic crisis when on pegzilarginase. This was because this had been informed by very few data points and implied that high peak ammonia levels would never happen in the pegzilarginase arm. The EAG provided a scenario analysis applying a continuity correction. This was applied by splitting 1 additional data point across all 4 peak ammonia categories for both the pegzilarginase and standard care arms. This added 0.25 to all observed values. The committee questioned whether hyperammonaemic crises occur in people whose condition is stabilised on pegzilarginase. The clinical experts highlighted that pegzilarginase reduces the severity of hyperammonaemic crisis. They added that they would not expect to see hyperammonaemic crises in people whose condition is controlled on pegzilarginase. The committee thought that it is likely that a few incidences of high levels of peak ammonia may still occur with pegzilarginase. But it thought that the values in the EAG's scenario were potentially too high. The committee requested a scenario in which the distribution of high levels of peak ammonia in the pegzilarginase arm was between the values used in the company's base case and EAG's scenario analysis. The company provided this at the second committee meeting. The EAG agreed that the analysis was implemented correctly,

but was still uncertain. The committee concluded the company's updated analysis was appropriate.

Utility values

Source of utility values

3.13 In the company's base case, health-state utility values were informed by data from the European burden of illness survey. This included EQ-5D-5L responses from 2 patients and 14 carers mapped to EQ-5D-3L using Hernandes Alava et al. (2023). For the GMFCS-1 health state, the company stated that the mapped EQ-5D-3L values were substantially lower than in similar health states for cerebral palsy and metachromatic leukodystrophy. Instead, the company used the mean of the utility value of the GMFCS-1 health state in the European burden of illness survey and general population utility at age 13 years. For the GMFCS-3 health state, the average of the GMFCS-2 and GMFCS-4 health-state utility values was used. The committee noted the EAG's scenario analysis that used the cerebral palsy utility values from Ryan et al. (2020), generated using ED-5D-Y, and considered whether these were more appropriate. The EAG explained that the company's utility values meant that some health states were assumed to be worse than death and queried whether this was plausible. The EAG noted that the utility values from Ryan et al. may have better face validity. But they noted these values had little impact on the cost-effectiveness estimates. At the second committee meeting, the committee noted that, in both the company's and EAG's base-case analyses, the total QALYs estimated for standard care were negative. The committee queried the validity of this. The committee concluded the health-state utility values used in the company's base case were appropriate for decision making, despite the uncertainty in these inputs.

Utility gain associated with improved diet

3.14 The company's submission highlighted that a higher proportion of people having pegzilarginase in the PEACE long-term extension had an increased protein consumption of more than 15% compared with placebo.

So, in its base case, it applied an average utility gain of 0.01 to the pegzilarginase arm for improved diet in a proportion of people who had increased dietary protein. This was estimated using a utility decrement reported in NICE's highly specialised technology guidance on volanesorsen for treating familial chylomicronaemia syndrome, a condition in which dietary fat levels must be restricted. The company assumed this utility decrement was generalisable to people having to restrict dietary protein. Clinical advice to the EAG supported the increase in utility for people eating more protein. But the EAG thought that this utility gain was uncertain. The EAG provided a scenario analysis in which zero utility gain was assumed for improved diet. The committee questioned the utility gain associated with improved diet, and whether dietary restrictions for people with arginase-1 deficiency are stricter than those for other metabolic conditions or conditions that need restricted diets. The clinical experts explained that people with arginase-1 deficiency have a more restricted diet than people with other conditions, adding that only about 50% of their protein intake is from natural food sources. But the clinical experts were unclear about how much liberalisation of diet there is with pegzilarginase treatment. The committee thought that the utility gain associated with increased dietary protein intake in the pegzilarginase arm was uncertain. But it recalled the evidence from PEACE showing increased dietary protein intake associated with pegzilarginase treatment.

At the second committee meeting, the company's base case included an increased proportion of people who had utility gains from a liberalised diet, from 24.7% to 83.3%. This was based on real-world evidence from France. The EAG highlighted that the actual proportion of people who gained 15% or more protein intake was not reported by the real-world evidence study. It added that a robust estimate could not be determined without additional information. The study reported that about 67% of people who had pegzilarginase for the first time increased protein intake by 15% or more. This suggested that the company's preferred 83.3% was too high. The EAG also noted that the real-world data was not adjusted for placebo effect. The EAG provided 2 scenarios in which:

- 48.5% of people had diet liberalisation (the 66.7% from the real-world evidence study, minus 18.2% for the placebo effect reported in PEACE)
- 24.7% of people had diet liberalisation (the company's original base case).

The company noted that healthcare professionals agreed that most people having pegzilarginase would have an improved diet. It noted that this did not necessarily mean their diet could be like that of the general population. But it did mean clinically important improvements. The clinical experts agreed and added that food restrictions are one of the most difficult aspects of the condition for people with arginase-1 deficiency. The patient experts also noted that standard care and a restrictive diet prevented children with the condition from living a normal life. The committee noted the substantial benefit people with the condition feel when they have more dietary choice. The committee thought that the value in the company's base case was too high because a placebo effect would have been appropriate. So, the committee concluded that applying a utility gain to 48.5% of people with diet liberalisation would be acceptable.

In response to the second draft guidance consultation, the company maintained its view that a health utility improvement of 0.04 should apply to 83.3% of people having pegzilarginase for diet liberalisation. At the third committee meeting, they reiterated that the trial placebo effect would not be sustained in the long term and is not supported by clinical practice. The clinical experts at the meeting explained that, in clinical practice, changes in diet with temporary increases in protein intake did occur. But this would result in increases in arginase levels, so people would need to return to their original restrictive diet. The patient expert at the third meeting also explained that being able to relax diet restrictions greatly improves quality of life, because it allows people to join in family meals and have a much wider range of foods. The EAG stated that people in the longer-term study may have changed their

behaviour because they knew they were being observed (known as the Hawthorne effect), rather than there being a true placebo effect. The committee noted that the size of utility benefit (0.04) was uncertain because the benefit is likely to vary from person to person. The committee accepted that people would unlikely be able to maintain a relaxed diet with current standard of care. It concluded that the company's assumption of applying a utility benefit of 0.04 to 83.3% of people taking pegzilarginase was appropriate for decision-making.

Disutility associated with cognitive disability

3.15 In its base case, the company assumed a relationship between GMFCS health state and cognitive impairment, as reported in HST18. The company thought that this was generalisable to people with arginase-1 deficiency having standard care. The company also assumed a distribution among cognitive ability categories for people in the GMFCS-1 health state. The company's model reflected this by using a disutility associated with cognitive disability that persisted indefinitely while people remained in each GMFCS health state. Cognitive disutility values in each GMFCS health state were estimated using values for metachromatic leukodystrophy presented in an Institute for Clinical and Economic Review report. For people having pegzilarginase, the company assumed that cognitive abilities would improve after 52 weeks. It used a different distribution to the standard care arm for the GMFCS-1 to GMFCS-3 health states. This was based on the small improvement in VABS-2 scores with pegzilarginase observed in the clinical studies. The company assumed no loss of utility in the no impairment and mild impairment cognitive ability categories. Clinical advice to the EAG was that the improvement in cognitive ability with pegzilarginase was plausible. But the EAG thought there was a lot of uncertainty related to this. The EAG provided a scenario analysis assuming that cognitive impairment by GMFCS health state was independent of treatment. The committee questioned whether cognitive disutility had already been captured by the GMFCS health-state utilities. The clinical experts explained that the cognitive impact of arginase-1 deficiency is associated with high ammonia levels rather than the type of

treatment. They further highlighted improvements in attention span, school results and communication with pegzilarginase. The company highlighted that, while evidence suggested cognitive improvement with pegzilarginase even in GMFCS-5, it only modelled this benefit for the GMFCS-1 to GMFCS-3 health states. The committee thought that the company's approach to applying treatment-specific cognitive disutility for GMFCS health states 1 to 3 was uncertain. But it also recognised that this approach was supported by clinical expert advice and may have been conservative. The committee concluded it was appropriate to apply treatment-specific cognitive disutility in GMFCS-1 to GMFCS-3 health states.

For the second committee meeting, the company updated its model so that cognitive progression was modelled independently to GMFCS health state. It also revised the categories for cognitive health states from 'none to mild', 'moderate' and 'severe' to 'no cognitive impairment', 'mild' and 'moderate to severe'. The transitions and utility values were also revised to reflect the updated cognitive impairment states. The company derived transitions between cognitive states for the standard care group from a regression analysis of data from the European burden of illness survey. The company stated that the regression analysis showed that, with time (increasing age), cognitive score declined while having standard care. For pegzilarginase, 'nominal' improvements were assumed for the first 36 months, after which people were assumed to remain in their current health states. The committee noted that the company had made substantive changes to how health utilities were estimated, and that this had not been requested by the committee. The EAG highlighted that no additional information was provided for the regression model or covariates used in the analysis, so these could not be validated. Also, the EAG noted that the coefficient from the regression analysis was not significant and was based on a small sample size, so the results were highly uncertain. The EAG stated that the updated utility values were overestimated in the 'no cognitive impairment' state. This resulted in a quality-of-life value close to full health (0.996). If people also had improved utility from diet

liberalisation (see section 3.14), their total utility would have exceeded 1 (which is not possible). Most importantly, the EAG stated that there was confounding between cognitive disutilities and GMFCS health states. It noted that the company did not appear to have considered or controlled for this. The EAG preferred the original methodology for cognitive disutilities presented at the first committee meeting. The committee concluded that the original approach of treatment-specific cognitive disutility applied to GMFCS health states was the more appropriate approach.

Carer disutility

3.16 In its base-case model, the company assumed people with arginase-1 deficiency need support from 2 carers up to age 16, followed by 1 carer after age 16. To reflect the impact on quality of life of carers, the company applied carer disutility from HST18 by collapsing GMFC-metachromatic leukodystrophy health states into GMFCS health states using clinical expert feedback. To account for uncertainty in the carer disutility values, the EAG explored 2 scenario analyses:

- It applied 0.062 carer disutility to carers of people in the GMFCS-3 health state and above, based on the difference between carers and the general population in the UK reported by Sevin et al. (2022). No carer disutility was assumed for people in GMFCS-1 or GMFCS-2.
- It pooled carer disutility values from the European burden of illness survey and disutility values for the GMFCS-4 and GMFCS-5 health states.

The committee considered the uncertainty in the carer disutility values but concluded that values used in the base-case model were acceptable for decision making.

For the second committee meeting, the company included an additional carer disutility for carers with more than 1 child with arginase-1 deficiency. The additional disutility was estimated from the European

burden of illness survey, based on the difference between utilities for carers with 1 child and carers with 2 or more children. The company also reported that the Delphi panel consensus was that 63% of children with arginase-1 deficiency also have a sibling with the condition. It added that disutility would be most significant from the GMFCS-3 health state onwards. The EAG agreed that there would be additional disutility when caring for more than 1 child with arginase-1 deficiency. But it noted that the data from the burden of illness survey had few data points, so lacked robustness and certainty. NICE's technical team highlighted that including this additional disutility resulted in double counting within the model, which already applied a carer disutility per child. The committee noted that there would be additional burden on carers looking after more than 1 child with arginase-1 deficiency. But it noted that the approach used by the company was not robust and led to double counting of carer disutility within the model. The committee concluded that no additional carer disutility should be applied.

Costs

Pegzilarginase dosing and drug wastage

3.17 At the first committee meeting, the company model assumed an average pegzilarginase dose of 0.14 mg/kg per week for the first 24 weeks, increasing to 0.16 mg/kg afterwards based on PEACE data. At the second committee meeting, the company updated this to reflect the longer-term extension study results (using 0.14 mg/kg throughout). It then applied a threshold patient weight of 10% or more for an additional vial of pegzilarginase. It thought that a margin of patient weight of 10% or less would not need an additional vial. The company limited the maximum dosage in the model to 0.2 mg/kg per week (as per the summary of product characteristics for pegzilarginase). This was because higher doses have not been tested in clinical trials. Clinical advice to the EAG noted that, while the company's base-case approach was appropriate, there would be concerted efforts to reduce drug wastage. This includes using an additional vial every 2 weeks should the optimal dose indicate

using half a vial a week. To account for the uncertainty in the level of drug wastage, the EAG provided scenario analyses. One of these assumed full drug wastage by removing the 10% margin and another assumed no drug wastage. At the second committee meeting, the company assumed that the adherence rate for pegzilarginase would follow that of PEACE and the longer-term extension (the exact rate is commercial in confidence and cannot be reported). The committee thought that the level of drug wastage, including the 10% weight margin, was uncertain but appropriate for decision making. It also thought that the company's assumptions for dose amount per kg and adherence rate were appropriate for decision-making but may differ between people with the condition.

Pegzilarginase weight-based dosing costs

3.18 The company calculated the number of vials of pegzilarginase needed at each age by assuming a constant weight ratio, compared with the general population at a given age. At the first committee meeting, NICE's technical team highlighted that the model assumed the same lower weight ratios from trials for people throughout the lifetime of the model. It considered whether the improved diet associated with pegzilarginase would allow people to gain weight and reach weights more in line with the expected general population weights. The team provided scenario analyses using heavier weights, including general population weights. One clinical expert highlighted that weight gain was seen in 1 person in PEACE and weight loss was seen when pegzilarginase was stopped at the end of the trial. The patient experts highlighted that improvement in a child's growth when having pegzilarginase could be linked to weight gain. The committee also noted that people needed to follow a restricted diet during the clinical trial's blinded phases (24 weeks in the randomised phase and initial 8 weeks in the long-term extension). The committee thought that the company's approach to weight-based dosing likely underestimated the costs of pegzilarginase. It thought that the technical team's scenario analyses using heavier weights were more plausible. It thought that assuming adults would weigh 95% of the expected general population weight was the most appropriate scenario presented.

At the second committee meeting, the company stated that a post-hoc analysis of PEACE data showed that, for people 13 years and over, there was no trend for increasing weight on pegzilarginase treatment compared with the general population. But it stated there was a trend for increasing weight in people under 13 years, in which weight tends to slowly approach that of the general population. It explained that because the model baseline age was 13 years, people would not have started treatment early enough to benefit. NICE's technical team noted that the average age in the model was 13 years, but there will be people below this age in NHS clinical practice who would have pegzilarginase. The team also noted that the company had modelled a higher percentage of females. The EAG highlighted that a systemic review (Bin Sawad et al. 2022) found that a roughly equal percentage of females and males would develop arginase-1 deficiency. The technical team also noted that the company modelled relatively high health-utility gains for pegzilarginase. This did not appear to align with a substantially underweight population. Responses to the draft guidance consultation from Metabolic UK and clinical experts stated that only a few people with the condition in the NHS in England are currently underweight. Also, results from a healthcare professional survey stated that several people gained weight on pegzilarginase treatment, including people who were underweight at baseline. The EAG provided a scenario analysis in which the weight of people having pegzilarginase was assumed to be 90% of the age-matched general population. It explained that this aligned with the company's clinical expert Delphi panel results. The committee concluded that the EAG's scenario analysis with the following assumptions were appropriate for decision making:

- people having pegzilarginase would weigh 90% of the general population weight
- 50% of people having pegzilarginase would be female.

In response to the second draft guidance, the company updated its base case to assume that 76% of the population having pegzilarginase

would be female. This was based on the proportion of females in the European burden of illness survey. The company stated this was appropriate because the committee had used this source to inform the starting distribution of people by GMFCS state in the model (see section 3.6). At the third committee meeting, NICE's technical team noted that the committee had used both the European burden of illness survey and information from the clinical survey submitted by Metabolic Support UK and clinical experts to inform starting distributions by health state. The team also highlighted another study (McNutt et al. 2025), a long-term extension study of pegzilarginase from 2 clinical trials (Study 102A and PEACE), which reported that 52% of patients were female. The clinical experts and patient expert at the meeting stated that most people who currently had the condition were female (around 70% to 75%). They explained that while the biology of the disease meant that it is equally likely to occur in males and females, the higher number of females in current NHS practice is likely a result of small numbers of patients with this rare condition and chance. In response to the second draft guidance, the company said that while it agreed with the committee that using 78% of general population weight (from the longer-term extension of pegzilarginase clinical trials in people aged 13 and above) may underestimate the average weight, 90% (the committee's preference from the second meeting) would overestimate weight. So, it adjusted its base case to assume people having pegzilarginase weighed 84% of the age- and sex-matched general population weight. It stated that this was the average of 78% and 90%. The company also outlined that the model starting age is 13 years, and that younger patients are more likely to benefit from improved growth with pegzilarginase. The clinical experts at the third committee meeting stated that in older patients, growth benefits are unlikely to be realised, and what constituted a healthier weight should be understood in the context of reduced height compared with the general population, that is, a relatively short population will have a proportionately lower healthy average weight. The clinical experts also outlined that dosing of pegzilarginase, while weight-based, is usually adjusted based on

plasma arginine levels over time. The committee noted that the company's model estimated drug costs by weight. The company stated that it did not believe a model based on plasma arginine levels would be possible, given the data limitations. The committee noted that drug costs may have been underestimated when assuming that people on pegzilarginase weigh 90% of the general population weight and that 76% are female. This was because the company used average weights by age ranges in the model, rather than using weight distributions, which the committee decided is more appropriate. This resulted in some weights in the model being just below the threshold for an additional vial of pegzilarginase. The EAG provided a scenario analysis that increased drug costs by 5% to account for this. But it highlighted that this may not be the most accurate amount, or the best method for adjusting costs. The committee acknowledged this scenario but preferred not to adjust costs in this way, given the uncertainty and input from clinical experts.

The committee concluded that a higher proportion of the current NHS population in England with the condition are female and accepted the company's assumption of 76%, although this may represent a small overestimate. The committee also preferred to assume that people on pegzilarginase would weigh 90% of the general population weight.

Pegzilarginase treatment discontinuation

3.19 In its base-case model, the company did not include a stopping rule for pegzilarginase because of a lack of consensus among the clinical experts it consulted. At the first committee meeting, the company thought that stopping of pegzilarginase would be low and assumed a 1% annual discontinuation rate in its base-case model. Clinical advice to the EAG agreed that it is unlikely that people would stop pegzilarginase when it is positively affecting plasma arginine levels. The EAG provided a scenario analysis that assumed no treatment discontinuation in the pegzilarginase arm. The committee noted a 4.8% pegzilarginase discontinuation rate in PEACE. This rate came from only 1 person who stopped pegzilarginase

early in the trial when having pegzilarginase by infusion in hospital. But in NHS clinical practice, people will be able to have subcutaneous injections of pegzilarginase from the start of treatment. NICE's technical team highlighted that the assumption about the rate of treatment discontinuation in the pegzilarginase arm had a large impact on the cost-effectiveness estimates. This was because a higher rate of treatment discontinuation than that in the base case substantially reduced the undiscounted QALYs gained in the pegzilarginase arm. This is a factor in deciding whether a QALY weighting should be applied (see section 3.20). The committee questioned if using 1% discontinuation in the model was appropriate. The clinical experts highlighted that subcutaneous injection would make using pegzilarginase treatment easier. They added that families engage with using this treatment. So, a low rate of pegzilarginase treatment discontinuation is plausible. The clinical experts also explained that 5% to 10% of adults could be expected to stop treatment over a 5-year period, and rates would be lower in children. The clinical expert submissions highlighted that it would be useful to have stop and start rules for pegzilarginase, which should be agreed with all specialist centres. The EAG noted that the company did not incorporate 'responders' and 'non-responders' in its base-case model to reflect pegzilarginase discontinuation. So, the committee questioned the practical application of pegzilarginase start and stop rules in NHS clinical practice. It also questioned whether this should be reflected in the economic model. The patient experts highlighted that, if pegzilarginase is stopped, health benefits are lost and the condition progresses. The committee noted that the rate of pegzilarginase discontinuation was very uncertain and likely relatively low. This is especially so because higher discontinuation rates are often used for other treatments. It concluded that a 2% pegzilarginase discontinuation was appropriate, but uncertain. The committee also concluded that the absence of an analysis based on responders and non-responders to pegzilarginase treatment in the model was acceptable. This was because this would be difficult to implement with the available data.

At the second committee meeting, the company had updated its base

case by fitting a Gompertz distribution to estimate treatment discontinuation. It thought that this distribution was the most appropriate because it estimated that around 92% of people would be on treatment after 1 year, with no discontinuations after this. It explained that this aligned with trial data and input from clinical experts. The EAG thought that it was highly unlikely that no discontinuations would occur after 1 year. The EAG preferred to use a log-logistic distribution as a more realistic estimation of treatment discontinuation. The committee agreed that the EAG's choice of distribution was the most appropriate for treatment discontinuation for pegzilarginase, but noted that this was highly uncertain.

QALY weighting

Criteria for applying a QALY weighting

3.20 NICE's manual on technology appraisal and highly specialised technologies guidance specifies that a most plausible incremental cost-effectiveness ratio (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 seen through the number of additional QALYs gained and by applying 'QALY weight'. The committee noted that NICE's manual on technology appraisal and highly specialised technologies guidance states that, for this weight to be applied, there needs to be compelling evidence that the treatment offers significant QALY gains. It is understood that a weight of between 1 and 3 can be applied when the QALY gain is between 11 and 29 QALYs. The committee noted that most of the company's and EAG's analyses showed QALY gains within this range. It also noted that the company included QALY losses associated with carer disutility in the QALY weight calculations. The EAG highlighted that it was unclear whether a calculation of incremental QALYs should include carer QALYs to estimate

QALY weighting. The EAG provided a scenario analysis removing QALYs associated with carers from the QALY weighting. The committee concluded that it was appropriate to remove carer disutility from the QALY weighting calculation. The committee agreed that there was evidence of significant QALY gains in most scenarios. But it thought that all these scenarios were associated with very high uncertainty about the robustness and likelihood of the QALYs generated by the model (see section 3.21). The committee considered accounting for this when applying the QALY weighting. The committee concluded that it could not apply the full QALY weighting as estimated by the economic model. This was primarily because of the very high uncertainty around key model parameters including:

- life expectancy for people having pegzilarginase (see section 3.11)
- whether disease progression occurs for some people on pegzilarginase (see section 3.7)
- how long people remain on pegzilarginase treatment (see section 3.19)
- the high quality-of-life gains for people having pegzilarginase compared with standard care (see sections 3.13 to 3.16).

The committee considered the input from the company and clinical experts on the benefits of pegzilarginase. This included the link between plasma arginine levels and clinical outcomes over the longer term. The committee also took into account the testimonies and evidence from patient experts and other stakeholders on the quality-of-life benefits offered by pegzilarginase. The committee, after considering this issue at 3 committee meetings, decided that it could not apply the full QALY weighting, as estimated by the economic model, because of the key model uncertainties outlined. These uncertainties had the potential to substantially increase the ICER estimates for pegzilarginase. The committee also noted that it had accepted, for the purposes of decision-making and considering the rarity of the condition (which may make evidence generation challenging), favourable assumptions for pegzilarginase in many aspects of the economic

modelling (which are listed above). These uncertainties, taken together, meant that the levels of uncertainty in the cost-effectiveness estimates were higher than those seen in other highly specialised technology evaluations. But the committee acknowledged that there was enough evidence to show that pegzilarginase could offer substantial QALYs for this population. So, it decided to apply a partial QALY weighting of 50%. The committee noted that this was a substantial weighting to apply to the QALYs in this evaluation. The exact level of weighting is commercial in confidence.

Cost-effectiveness estimates

The committee's preferred assumptions

3.21 Because of the uncertainty in many model inputs, the committee considered several scenarios. While it thought that some of these scenarios were plausible, it noted the very high level of uncertainty. The committee acknowledged that much of the uncertainty was because of small clinical studies of short duration and strong assumptions made in the economic model. It took this into consideration. For the purposes of decision making, when possible, the committee selected what were likely to be the most reasonable preferred assumptions. These were:

- distributions in each GMFCS health state informed by the European burden of illness survey, but assuming 50% of people in the GMFCS-2 health state would be in GMFCS-3 instead (see section 3.6)
- everyone in the pegzilarginase arm remaining in the same GMFCS health state after 3 years (see section 3.7)
- for transitions between different health states in the standard care arm:
  - using the mean of PEACE, Study 101A and Study 102A as the starting GMFM-DE score for people in the GMFCS-1 health state (see section 3.8)
  - a reduction in GMFM-DE score of 2.66 per year (see section 3.8)
  - converting inverse of time spent in a GMFCS health state to a probability (see section 3.8).

- the EAG's preferred analysis that 5% of people per year transition from the GMFCS-2 and -3 health states to GMFCS-5 after hyperammonaemic crisis in people under 16 years, in both the pegzilarginase and standard care arms (see section 3.9)
- standardised mortality rates for the pegzilarginase arm and standard care used in the EAG's preferred analysis, with the GMFCS-2 health state for pegzilarginase having a standardised mortality ratio equal to 25% of that for standard care (see section 3.11)
- GMFCS health-state utility values used in the company's base case (see section 3.13)
- utility gain associated with improved diet with pegzilarginase treatment is applied to 83.3% of people (see section 3.14)
- treatment-specific cognitive disutility applied in the GMFCS-1 to GMFCS-3 health states (see section 3.15)
- carer disutility as applied in the company's base case but not applying additional carer disutility for carers with more than 1 child with the condition (see section 3.16)
- the company's adherence rate, a dosing amount of 0.14 mg/kg and a 10% threshold for drug wastage (see section 3.17)
- adults having pegzilarginase would weigh 90% of the general population weight, and 76% of people with the condition in the NHS in England are expected to be female (see sections 3.17 and 3.18)
- using the EAG's log-logistic distribution for pegzilarginase treatment discontinuation (see section 3.19)
- applying a QALY weighting equal to 50% of the QALY weighting implied by the economic model using the committee preferences listed above (see section 3.20).

  Using the committee's preferred assumptions and an updated price for pegzilarginase provided after the third committee meeting, the probabilistic ICER estimate was £99,256 (assuming 50% of the QALY weighting implied by the economic model) for pegzilarginase compared

with standard care. This is within the range that NICE considers an acceptable use of NHS resources for highly specialised technologies.

Other factors

Equality

3.22 The patient carer organisation stated that arginase-1 deficiency is a genetic condition with a reported higher prevalence in communities in which consanguineous marriage is more prevalent. It highlighted that special consideration must be given to communities in which consanguineous marriage is common. The committee considered this issue. It also thought that its recommendation applied equally and difference in condition prevalence does not in itself represent an equality issue. The committee concluded that there were no equalities issues that could be addressed by its recommendations.

Uncaptured benefits

3.23 The committee considered whether there were any uncaptured benefits of pegzilarginase. It did not identify additional benefits of pegzilarginase not captured in the economic modelling. So, the committee concluded that all additional benefits of pegzilarginase had already been taken into account.

Conclusion

Recommendation

3.24 The clinical-effectiveness evidence for pegzilarginase was uncertain because the clinical studies were small and of short duration. There were also several areas of uncertainties in the economic model. Despite this, the most likely cost-effectiveness estimates for pegzilarginase are within the range that NICE considers an acceptable use of NHS resources for highly specialised technologies. So, pegzilarginase can be used, within its marketing authorisation, for treating arginase 1 deficiency (also called hyperargininaemia) in people 2 years and over.

4 Implementation

4.1 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 integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days of its date of publication.

4.2 Section 4f of The Innovative Medicines Fund Principles states that a discretionary source of early funding (from the overall Innovative Medicines Fund budget) is available for certain medicines recommended by NICE. In this instance, interim funding has been agreed for pegzilarginase. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets.

4.3 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 60 days of the first publication of the final draft guidance.

4.4 When NICE recommends a treatment ‘as an option’, the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has arginase-1 deficiency and the healthcare professional responsible for their care thinks that pegzilarginase is the right treatment, it should be available for use, in line with NICE’s recommendations.

5 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 being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

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.

Chair

Paul Arundel
Chair, highly specialised technologies evaluation committee

NICE project team

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

Zain Hussain and Lauren Elston
Technical leads

Alan Moore
Technical adviser

Vonda Murray and Thomas Feist
Project managers

Richard Diaz
Associate director

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