NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

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

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using pegzilarginase in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

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

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

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: August 2024

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

After consultation:

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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using pegzilarginase in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 27 September 2024
- Second evaluation committee meeting: To be confirmed
- Details of membership of the evaluation committee are given in section 4

1 Recommendations

1.1 Pegzilarginase is not recommended, within its marketing authorisation, for treating arginase-1 deficiency (also called hyperarginaemia) in people 2 years and over.

1.2 This recommendation is not intended to affect treatment with pegzilarginase that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop. For children or young people, this decision should be made jointly by the healthcare professional, the child or young person, and their parents or carers.

Why the committee made these recommendations

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.

There are also several uncertainties in the economic model, including:

- whether the number of people grouped by disease severity is similar to that in NHS clinical practice
- assumptions on how age varies in NHS clinical practice at the start of each disease severity group
- how pegzilarginase affects body weight and levels of ammonia in the blood
- how long people stay on pegzilarginase treatment.

Because of the uncertainties in the clinical evidence and economic model, the most likely cost-effectiveness estimates are substantially above the range that NICE considers an acceptable use of NHS resources for highly specialised technologies. So, pegzilarginase is not recommended.

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 (simple discount patient access scheme), which would have applied if pegzilarginase had been recommended. The size of the discount is commercial in confidence.

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 disease 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 morbidity, 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 associated with multiple comorbidities, poor survival, and a substantial impact on quality of life for patients and 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 long-term management of arginase-1 deficiency alongside individualised disease management. Clinical experts highlighted that the disease 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. 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 considered 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. All people 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 and 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 and 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 was not routine practice in the NHS, but in some trial locations patients 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% and 4.1% for the pegzilarginase arm and placebo arm, respectively. The least squares mean difference between treatment arms was 6.0% (95% confidence interval [CI]: -19.6%, 31.6%; p=0.6409).
- The least squares estimates of the mean change from baseline in GMFM-E score for the pegzilarginase arm and placebo arm at week 24 were 3.5 (95% CI: 1.2, 5.8) and -1.1 (95% CI: -5.3, 3.2), respectively. The least squares mean difference between treatment arms was 4.6 (p=0.0703).

- The least squares estimates of the mean change from baseline in GMFM-D score for the pegzilarginase arm and placebo arm were 2.2 (95% CI: 1.2, 3.2) and 0.0 (95% CI: -2.0, 1.9), respectively. The least squares mean difference between treatment arms was 2.2 (p=0.0504).

The EAG highlighted that pegzilarginase appears to have a large effect on plasma arginine levels within the first 24 weeks. However, 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 patient numbers (see section 3.3). However, the EAG explained about the plausible ceiling effect for mobility and spasticity outcomes. 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 committee further heard from the clinical experts that plasma arginine level is an appropriate surrogate outcome despite not being the only marker for disease severity. The committee was also aware that some outcomes, such as the 2-minute walk test, may not be informative of how treatment is modelled. The committee noted the absence of survival data presented in the company submission. The clinical experts explained that despite the lack of survival data from the clinical trials, it is plausible for pegzilarginase to extend survival, although the extension to life was uncertain. The committee concluded that pegzilarginase reduces plasma arginine levels, an important outcome in the pathogenesis of arginase-1 deficiency. However, life extension with pegzilarginase was uncertain, given the lack of longer-term data.

Economic model

Company's modelling approach

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 (from now, pegzilarginase) or individualised disease management alone (from now, standard care). People in the model progressed through different health states, which 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, requiring hospitalisation or emergency department management. Hyperammonaemic crises were associated with increased healthcare costs and worsening of patient 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 NICE technical team highlighted that the company's base case used the same starting age across all GMFCS health states (the exact value is considered confidential by the company and cannot be reported here). They explained that this is likely inconsistent with the prevalent NHS cohort in which it is expected that younger people would be in less severe GMFCS health states and older people would be in more severe GMFCS health states. The committee thought that the company's current modelling approach does not reflect age at each GMFCS health state in clinical practice. The committee concluded it would like to see the results of an alternative modelling approach as a scenario analysis, in which mean starting age varies according to the GMFCS health state. This is because this would likely be a more appropriate modelling of the condition.

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 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 underrepresent 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 in the economic model. 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 diagnosis of arginase-1 deficiency was to improve, a larger distribution of the modelled population would be 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 around 50% of people with the condition are adults. The committee considered that the starting distributions from the European burden of illness survey is more representative of clinical practice in the NHS in England 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 is because starting distributions have the potential to substantially impact cost-effectiveness estimates.

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 remain 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 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 considered it plausible that people on pegzilarginase remain in the same GMFCS health state after 3 years. However, the EAG highlighted that this assumption is very uncertain because it solely relies upon clinical expert opinion. The EAG further explained that PEACE only reported data on mobility outcomes for a short period of time. The clinical experts considered that the company's assumption that people on pegzilarginase remain in the same GMFCS health state after 3 years is 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 considered that this may be difficult to capture in the economic model. The company further highlighted that at 3 years, approximately 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 considered that the company's assumption that people in the pegzilarginase arm remain in the same GMFCS health state after 3 years is very uncertain. But in the absence of longer-term clinical trial evidence, it relied upon clinical expert opinion that the company's assumption is plausible. The committee concluded that assuming people in the pegzilarginase arm remain in the same GMFCS health state after 3 years is appropriate for decision making, but this was associated with 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, which the company assumed to be generalisable for 26 weeks. Long-term transition probabilities for the standard care arm beyond 24 weeks were estimated using the relationship between GMFCS health state and combined GMFM-DE score. The company assumed thresholds for change between GMFCS health states as the midpoint between the lower confidence intervals for better GMFCS health states and upper confidence intervals for worse GMFCS health states. When calculating the transition probabilities for progressing from the GMFCS-1 to GMFCS-2 health state, the company assumed a combined GMFM-DE score (the exact value is considered confidential by the company and cannot be reported here) for people in the GMFCS-1 health state. 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 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 is unlikely because it suggests that people can have arginase-1 deficiency without deterioration in GMFM-DE score, which is unlikely. 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 further noted that a yearly reduction in GMFM-DE score of 1.45 meant that the estimated time to move from the GMFCS-1 to GMFCS-5 health state is considerably higher than clinical expert predictions (the exact value is considered confidential by the company and cannot be reported here). Instead, the EAG used the upper limit of 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 is more aligned with clinical estimates. The EAG also provided a scenario analysis in which transition probabilities between GMFCS health states in the standard care arm were associated with the time in a GMFCS health state. These were calculated using the midpoint of the GMFM-DE score for each GMFCS health state. The clinical experts explained that it would take approximately 20 years to progress from the GMFCS-1 to GMFCS-5 health states in clinical practice without pegzilarginase treatment. The company highlighted that the EAG's scenario analysis is counterintuitive. This is because it results in transition probabilities for the GMFCS-1 and GMFCS-2 health states that are higher than transition probabilities for the GMFCS-4 and GMFCS-5 health states. The committee considered that the EAG's base-case approach to model transition probabilities for the standard care arm are more reflective of clinical expert estimates of the time taken to progress to more severe GMFCS health states. For modelling transition probabilities in the standard care arm, the committee considered the following conclusions were appropriate for decision making:

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

Mortality

Life expectancy

3.9 In its base case, the company adjusted the economic model so that nearly all people in the standard care arm die by age 35, including death associated with hyperammonaemic crisis. To apply this adjustment the company made the following assumptions:

- Using the standardised mortality rates from metachromatic leukodystrophy 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 were generalisable for people with arginase-1 deficiency having pegzilarginase, after removing the toxicity associated with the treatment for metachromatic leukodystrophy (atidarsagene autotemcel).
- Obtaining 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 pegzilarginase arm. This resulted in 0.0008% of people alive at age 35 in the standard care arm. Clinical advice to the EAG suggested that it was unlikely that nearly all people would die by age 35. The EAG noted that 1 patient in the European burden of illness survey was aged 49. To address the uncertainty in the standardised mortality rate for the pegzilarginase arm and the company's assumption that nearly all people

in the standard care arm die by age 35, the EAG provided following scenario analyses:

- Assuming the standardised mortality rate for the pegzilarginase arm is 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 for pegzilarginase arm.
- Assuming that nearly all people died before age 50 in the standard care arm and that all people were aged 4 years at the start of the model. This took into account that some people may have died between age 4 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.
- Assuming a calibration based on starting age that resulted in a standardised mortality rate in which 0.0033% of people were alive at age 35 (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 age 35 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 and whether the EAG's scenario analysis doubling 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 is 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 even 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. Therefore, standardised mortality rate was considered 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 scenario analyses by GMFCS subgroups. The EAG explained that these analyses were not recalibrated and mortality in the model was driven by hyperammonaemic crises which are independent of GMFCS health states. The committee considered there is considerable uncertainty in how mortality is modelled in the company's base-case approach. It recalled clinical expert advice that people would be expected to live longer than 35 years with improved clinical management for arginase-1 deficiency and that hyperammonaemic crises drives 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 this was uncertain because of the small standardised mortality rates and similar results by GMFCS subgroup. The committee requested further analyses around mortality in the model, including 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 all people in the standard care arm die at age 50 is appropriate.

Distribution of peak ammonia levels during hyperammonaemic crisis

3.10 In the company's base-case model, a proportion of hyperammonaemic crises are 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. (2002), the Urea Cycle Disorders Consortium registry and the placebo arm of PEACE (the number of episodes are 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 is considerable uncertainty around the peak ammonia levels during a hyperammonaemic crisis when on pegzilarginase. This is because this has been informed by very few data points and implies that high peak ammonia levels would never happen in the pegzilarginase arm. The EAG provided a scenario analysis by applying a continuity correction, operationalised by splitting 1 additional data point across all 4 peak ammonia categories for both the pegzilarginase and standard care arms, which adds 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 and that hyperammonaemic crises do not occur in people whose condition is controlled on pegzilarginase. The committee considered that it is likely that a few incidences of high levels of peak ammonia may still occur with pegzilarginase but 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 is between the values used in the company's base case and EAG's scenario analysis.

Utility values

Source of utility values

3.11 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. 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 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 if this was plausible. The EAG noted that while utility values from Ryan et al. may have better face validity, they had little impact on the cost-effectiveness estimates. The committee concluded the health state utility values used in the company's base case are appropriate for decision making.

Utility gain associated with improved diet

3.12 The company submission highlighted that a reasonable proportion of people having pegzilarginase in the PEACE long-term extension had an increased protein consumption of more than 15% compared with baseline. So, it applied an average utility gain of 0.01 to the pegzilarginase arm in its base case as a result of 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 technologies guidance on volanesorsen for treating familial chylomicronaemia syndrome, a condition in which dietary fat levels must be restricted. The company assumed this loss was generalisable to people having to restrict dietary protein. Clinical advice to the EAG supported the increase in utility for people eating more protein. However, the EAG considered this utility gain was uncertain. The EAG provided a scenario analysis in which zero utility gain is assumed for improved diet. The committee questioned the utility gain associated with improved diet. It was concerned whether dietary restrictions for people with arginase-1 deficiency are any more strict 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 and only about 50% of their protein intake is from natural food sources. However, the clinical experts were unclear how much liberalisation of diet there is with pegzilarginase treatment. The committee considered that the utility gain associated with increased dietary protein intake in the pegzilarginase arm is uncertain. But it recalled the evidence from PEACE showing increased dietary protein intake associated with pegzilarginase treatment. The committee concluded that the company's assumed utility gain associated with improved diet in the pegzilarginase arm is appropriate for decision making.

Disutility associated with cognitive disability

3.13 In its base case, the company assumed a relationship between GMFCS health state and cognitive impairment as reported in NICE's highly specialised technologies guidance on atidarsagene autotemcel for treating metachromatic leukodystrophy. The company considered this was generalisable to people with arginase-1 deficiency having individualised disease management. The company also assumed a distribution among cognitive ability categories for people in the GMFCS-1 health state. The company model reflected this by using a disutility associated with cognitive disability that persisted indefinitely while people remain 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 and 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 considered that the improvement in

cognitive ability with pegzilarginase was plausible. But the EAG considered that there is a large degree of uncertainty related to this. The EAG provided a scenario analysis assuming that cognitive impairment by GMFCS health state is 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. The experts 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 considered that the company's approach to applying treatment-specific cognitive disutility for GMFCS health states 1 to 3 is uncertain. But it also recognised that this approach is supported by clinical expert advice and may be conservative. The committee concluded it is appropriate to apply treatment-specific cognitive disutility in GMFCS-1 to GMFCS-3 health states.

Carer disutility

3.14 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 the evaluation of atidarsagene autotemcel for treating metachromatic leukodystrophy 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:

- Applying 0.062 carer disutility to carers of people in the GMFCS-3 health state and above, based on difference between carers and population norm in the UK reported by Sevin et al. (2022). No caregiver disutility was assumed for people in GMFCS-1 or GMFCS-2.

- Pooling of 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 are acceptable for decision making.

Costs

Pegzilarginase dosing and drug wastage

3.15 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. It then applied a threshold patient weight of 10% or more for an additional vial of pegzilarginase. It considered a margin of patients weight of 10% or less would not need an additional vial. The number of vials required at each age were calculated assuming a constant weight ratio, compared with the general population at a given age. 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), 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 a scenario analysis assuming full drug wastage by removing the 10% margin and another assuming no drug wastage. The NICE technical team highlighted that the model assumes 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 achieve weights that are more in line with the expected general population weights. The NICE technical team provided scenario analyses using heavier weights, including general population weights.

One clinical expert highlighted that weight gain was observed in 1 patient in PEACE and weight loss was observed when pegzilarginase was stopped at the end of the trial. The patient expert highlighted that improvement in a child's growth when having pegzilarginase could be linked to weight gain. The committee also noted that people were required to follow a restricted diet during the clinical trial blinded phase (24 weeks in the randomised phase and initial 8 weeks in the long-term extension). The committee considered that the company's approach to weight-based dosing is likely to underestimate the costs of pegzilarginase. It believed that the NICE technical team's scenario analyses using heavier weights are more plausible. It considered that assuming adults would weigh 95% of the expected general population weight was the most appropriate scenario presented. The committee also considered that the level of drug wastage, including 10% weight margin, is uncertain. The committee concluded that the company's approach of using constant weight ratio (compared to general population weight) based on trial baseline for all patients to calculate pegzilarginase dose over the model lifetime is not appropriate. The committee requested data (from trials and clinical expert opinion) on the impact of pegzilarginase on weight over someone's lifetime.

Pegzilarginase treatment discontinuation

3.16 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. However, the company considered that discontinuation 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 people would stop pegzilarginase when it was positively impacting plasma arginine levels. The EAG provided a scenario that assumed no treatment discontinuation in the pegzilarginase arm. The committee noted a 4.8% pegzilarginase discontinuation rate in PEACE. But it was aware that this rate came from only 1 person who stopped pegzilarginase early in the trial when having pegzilarginase by infusion in hospital. However, in

clinical practice, people will be able to have subcutaneous injections of pegzilarginase from the start of treatment. The NICE technical team highlighted that the assumption around the rate of treatment discontinuation in the pegzilarginase arm has a large impact on the cost-effectiveness estimates. This is because a higher rate of treatment discontinuation than that in the base case substantially reduces the undiscounted quality-adjusted life years (QALYs) gained in the pegzilarginase arm, which is a factor in deciding whether a QALY weighting should be applied (see section 3.17). The committee questioned if using 1% discontinuation in the model was appropriate. Clinical experts at the meeting highlighted that subcutaneous injection would make pegzilarginase treatment easier and families are often more engaged. So, a low rate of pegzilarginase treatment discontinuation is plausible. The committee further heard from the clinical experts that 5% to 10% of adults could be expected to stop treatment over a 5-year period, with rates 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 also 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 clinical practice and whether this should be reflected in the economic model. Patient experts highlighted that if pegzilarginase is stopped, health benefits are lost and the condition progresses. The committee considered that the rate of pegzilarginase discontinuation is very uncertain and likely relatively low, especially because higher discontinuation rates are often used for other treatments. It concluded that a 2% pegzilarginase discontinuation is 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 is acceptable because this would be difficult to implement with the available data.

QALY weighting

Criteria for applying a QALY weighting

3.17 NICE's health technology evaluations manual (2022) 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 health technology evaluations manual 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 is unclear if 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 recalled that for a QALY weight to be applied, there will need to be compelling evidence that the treatment offers significant QALY gains. It agreed that there was evidence of significant QALY gains in most scenarios. But it considered all of these scenarios were associated with very high uncertainty about the robustness and likelihood of the QALYs generated by the model (see section 3.19). The committee considered accounting for this when applying the QALY weighting. The committee concluded that it was appropriate to remove carer disutility from the QALY weighting calculation. The committee concluded that it could not apply a QALY weighting at this stage because of the high uncertainty around key model

parameters. It requested further input on these from consultation with stakeholders.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.18 The company's base case showed that pegzilarginase was associated with a probabilistic ICER of £568,635 per QALY gained compared with standard care. In the EAG's base case, pegzilarginase was associated with a probabilistic ICER of £558,411 per QALY gained compared with standard care. All reported ICERs included the confidential discount for pegzilarginase available to the NHS. The committee noted that applying a QALY weighting has a significant impact on the cost-effectiveness estimates, resulting in substantially lower probabilistic base-case ICERs in both the company's and EAG's analyses. However, the committee considered that it could not apply a QALY weighting because of the high uncertainty around key model parameters (see section 3.17).

The committee's preferred assumptions

3.19 Because of the uncertainty in many model inputs, the committee considered several scenarios. While it considered some of these scenarios to be plausible, it noted the very high level of uncertainty. The committee acknowledged that much of the uncertainty is because of small clinical studies of short duration, as well as strong assumptions made in the economic model, and 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 (see section 3.6)
- all people 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)
  - 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)
- standardised mortality rates for the pegzilarginase arm used in the company's base case (see section 3.9)
- nearly all people in the standard care arm die at age 50 (see section 3.9)
- GMFCS health state utility values used in the company's base case (see section 3.11)
- utility gain associated with improved diet with pegzilarginase treatment is appropriate (see section 3.12)
- treatment-specific cognitive disutility applied in the GMFCS-1 to GMFCS-3 health states (see section 3.13)
- carer disutility as applied in the company's base case (see section 3.14)
- assuming that adults having pegzilarginase would weigh 95% of the general population weight (see section 3.15)
- 2% annual pegzilarginase discontinuation (see section 3.16).

The committee considered that there were additional uncertainties that it wants to see further input on. The committee also questioned the appropriateness of several model inputs informed by previous NICE highly specialised technologies evaluations (see section 3.9 and sections 3.11 to 3.14). The committee requested:

- data on the current population with arginase-1 deficiency in the NHS in England (see section 3.6)
- a revised modelling approach, in which mean age varies according to the GMFCS health state (see section 3.5)

- further analysis around standardised mortality rates in the model (see section 3.9)
- additional data (from trials and clinical expert opinion) on the impact of pegzilarginase treatment on patient weight (see section 3.15)
- a scenario in which distribution of high levels of peak ammonia in the pegzilarginase arm is between the values used in the company's base case and EAG's scenario analysis (see section 3.10)
- clinical input on the relevance of metachromatic leukodystrophy and familial chylomicronaemia syndrome to arginase-1 deficiency (see section 3.9 and sections 3.11 to 3.14).

Using the committee's preferred assumptions, the most likely cost-effectiveness estimates for pegzilarginase are substantially above the range that NICE considers an acceptable use of NHS resources for highly specialised technologies.

Managed access

Recommendation with managed access

3.20 The committee noted that the company had not submitted a managed access proposal and there were no sources of data collection that would allow a managed access proposal. So, the committee could not make a recommendation for managed access at this stage.

Other factors

Equality

3.21 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 considered that its recommendation applies 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

3.22 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

3.23 The clinical-effectiveness evidence for pegzilarginase is uncertain because the clinical studies were small and of short duration. There are also several areas of uncertainties in the economic model, some of which are unresolved. The most likely cost-effectiveness estimates for pegzilarginase are substantially above the range that NICE considers an acceptable use of NHS resources for highly specialised technologies. So, pegzilarginase is not recommended.

4 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

Technical lead

Alan Moore

Technical adviser

Vonda Murray

Project manager

Richard Diaz

Associate director

ISBN: [to be added at publication]