NICE National Institute for Health and Care Excellence

NICE guidance

Eladocagene exuparvovec for treating aromatic L-amino acid decarboxylase deficiency

Highly specialised technologies guidance

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Your responsibility

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

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

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

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

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1 Recommendations

1.1 Eladocagene exuparvovec is recommended, within its marketing authorisation, as an option for treating aromatic L-amino acid decarboxylase (AADC) deficiency in people 18 months and over with a clinical, molecular and genetically confirmed diagnosis of AADC deficiency with a severe phenotype. Eladocagene exuparvovec is only recommended if the company provides it according to the commercial arrangement.

Why the committee made these recommendations

AADC deficiency is a rare genetic disorder that causes a wide range of debilitating symptoms. Normal motor development in young children (such as head control, sitting and walking with help) is particularly affected. Severe AADC deficiency is associated with a high risk of death in childhood. It also has a substantial effect on the quality of life of the person with the condition, and their family and carers. Current treatments only manage the symptoms of AADC. There are no specific treatments for the condition.

The clinical evidence suggests that eladocagene exuparvovec improves motor development, and that these improvements will last. But the results are uncertain because the studies are very small, and provide limited long-term data and limited information about non-motor outcomes.

Even taking this uncertainty into account, the cost-effectiveness estimates for eladocagene exuparvovec are within the range that NICE considers an effective use of NHS resources for highly specialised technologies. So, eladocagene exuparvovec is recommended for routine use in the NHS.

2 Information about eladocagene exuparvovec

Marketing authorisation indication

2.1 Eladocagene exuparvovec (Upstaza, PTC Therapeutics) is indicated for the 'treatment of patients aged 18 months and older with a clinical, molecular, and genetically confirmed diagnosis of aromatic L-amino acid decarboxylase (AADC) deficiency with a severe phenotype'.

Dosage in the marketing authorisation

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

Price

2.3 The price for a 0.5 ml solution for infusion of eladocagene exuparvovec is £3,010,451 (excluding VAT; company submission).

2.4 The company has a commercial arrangement. This makes eladocagene exuparvovec available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The evaluation committee considered evidence submitted by PTC Therapeutics, 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

Aromatic L-amino acid decarboxylase deficiency

3.1 Aromatic L-amino acid decarboxylase (AADC) deficiency is an ultra-rare genetic disorder. It is associated with a wide range of severe symptoms mainly affecting the central nervous system, autonomic nervous system, gastrointestinal system and endocrine system. It is caused by a mutation in the DDC gene. This results in a lack of the AADC enzyme, which leads to severe deficiency in dopamine and other neurotransmitters essential for normal development. Dopamine deficiency is considered to be key in the pathology of AADC deficiency. It is also the precursor for adrenaline and noradrenaline. Lack of these neurotransmitters is known to affect mood, attention, sleeping habits and learning. Serotonin deficiency is also known to contribute to symptoms of the condition, although the extent of its role relative to dopamine is uncertain. AADC deficiency typically presents from birth, with symptoms becoming apparent in the first few months of life. The condition is often difficult to diagnose because of its rarity and the wide range of possible symptoms. The mean age at diagnosis is usually around 3.5 years, but can range from 2 months to 23 years. AADC deficiency is characterised by oculogyric crises, which are episodes of involuntary muscle spasm that results in upwards deviation of the eyes. These episodes can last several hours, and people with the condition are often misdiagnosed as having epilepsy, which can delay appropriate treatment. In the UK, a final diagnosis is often confirmed through genetic testing of the DDC gene. About 80% of people with AADC deficiency present with a severe phenotype, broadly defined by international consensus guidelines as reaching no or very limited developmental milestones, and full dependence on carers. The company's submission proposed that a severe phenotype may also be defined as having no or poor head control at 24 months of age. In very severe cases, people may be bedridden with little or no motor function, and be at high risk of premature death within the first 2 decades of life. Because of the rarity of AADC deficiency, there is little evidence about its effect on survival. But clinical expert opinion suggests that most people die within the first decade of life. Causes of death vary, but include comorbidities associated with the condition such as multiple organ failure, pneumonia, acute complications during an oculogyric crisis episode and asphyxia. The committee noted that AADC is a spectrum of conditions, and that most people present with a severe phenotype.

Effects of AADC deficiency

3.2 The patient experts explained that the most common characteristic of AADC deficiency is lack of motor development. Over 95% of people have very limited motor function and do not reach key motor milestones. Many children with severe AADC deficiency are unable to hold their head up, sit by themselves, stand or speak. These limitations mean they are often unable to participate in activities that children of a similar age without the condition can do, such as playing with toys, feeding themselves or attending school. As well as a lack of motor development, people with the condition may cry and sweat excessively, have sleep problems, irritability and mood disorders, problems with digestion, and delayed language and communication skills. Feeding problems are a common symptom of AADC deficiency, with many needing tube feeding because of difficulties with swallowing, a risk of choking, and a general disinterest in food. This means that people with AADC deficiency can be below average weight for their age, or have impaired nutrition. Oculogyric crises can be frequent, painful and long in duration, lasting up to 8 hours or more. During an oculogyric crisis, the eyes typically roll upward without control and there is tongue thrusting, jaw spasms, hyperextension of the head, neck and back, and involuntary muscle contractions. This is very distressing for young people with AADC deficiency and their families. AADC deficiency can severely affect the quality of life of people with the condition, and their families and carers, who often must provide round-the-clock care. Carers report a profound emotional effect, including depressive symptoms, sadness and anxiety. They also say that it affects their career, family relationships and social lives. Everyday life is also affected by the need for frequent healthcare visits as well as hospital admissions for acute complications. The committee concluded AADC is a serious condition that has a substantial effect on the quality of life of those with the condition, and of family members and carers.

Clinical management

Treatment options

3.3 There are currently no disease-modifying treatments for AADC deficiency. Because there are no relevant guidelines on AADC deficiency in the UK and no specifically licensed treatments, current best practice is best supportive care. This is highly individualised to the specific symptomatic needs of the child. Management focuses on symptom control using an extensive list of medicines. It involves multidisciplinary team support from specialists, including paediatric neurologists, gastrointestinal specialists, respiratory specialists, endocrinologists, orthopaedic surgeons, speech therapists, and physical and occupational therapists. The most commonly used symptomatic treatments all target the dopamine pathway. They include dopamine receptor agonists (to activate postsynaptic dopamine receptors), monoamine oxidase inhibitors (to prevent the breakdown of dopamine and serotonin), and pyridoxine plus pyridoxal phosphate (to increase the activity of the AADC enzyme). None of these symptomatic treatments directly correct the underlying cause of AADC deficiency.

The unmet need

3.4 The patient experts highlighted that there is an unmet need for disease-modifying treatments for AADC deficiency. They highlighted that eladocagene exuparvovec has the potential to offer substantial and potentially transformative benefits to people with AADC deficiency, and their family and carers, including the single-dose administration. This is because it would likely reduce the need for additional symptomatic treatments and medications, and avoid the need for regular travel for treatment. The patient experts expressed some concern about the need for administration of the treatment through brain surgery that is not without inherent risks. They also pointed out that eladocagene exuparvovec does not address the deficiency of serotonin. But they thought that this technology has the potential to address some of the unmet needs of people with AADC deficiency, and will treat the underlying condition rather than the symptoms. The committee concluded that people with the condition, and their families and carers, would welcome eladocagene exuparvovec as a treatment option for AADC deficiency.

Comparators

3.5 There is no active treatment routinely commissioned in clinical practice in England for AADC deficiency. So, the committee accepted that best supportive care was the relevant comparator for this evaluation.

Clinical effectiveness

Clinical trial evidence

3.6 The main clinical-effectiveness evidence for eladocagene exuparvovec came from 3 open-label single-arm studies carried out in Taiwan (AADC-010, AADC-011 and AADC-CU/1601). They included a total of 28 people with a confirmed diagnosis of severe AADC deficiency (10, 12 and 8 people respectively). The company's submission defined a severe phenotype as no or poor head control by 2 years. There is a median of 5 years of follow-up data from AADC-010 and AADC-CU/1601, and 1 year of follow-up data from AADC-011. In AADC-CU/1601 and AADC-010, everyone had a $1.8x10^{11}$ vector genomes (vg) dose of eladocagene exuparvovec. In AADC-011, 3 people had $1.8x10^{11}$ vg and 9 people had a $2.4x10^{11}$ vg dose of eladocagene exuparvovec. The European Medicines Agency and a clinical expert consulted by the EAG considered the 2 doses to be equivalent in terms of safety and efficacy. They also thought that it was appropriate to consider the results of both doses together. The summary of product characteristics for eladocagene exuparvovec states that 'patients will receive a total dose of $1.8x10^{11}$ vg delivered as four 0.08 ml ($0.45x10^{11}$ vg) infusions (two per putamen)'. The primary outcome in each study was the proportion of people who reached the key motor milestones of full head control, sitting unassisted, walking with assistance, and standing with support. These were measured using a well-established measure of child motor development, the Peabody Developmental Motor Scales Second Edition (PDMS-2). The primary outcome time point was 60 months in AADC-010 and AADC-CU/1601, and 12 months in AADC-011. Secondary outcomes measured in the trials included:

- development and motor function (as measured by the Alberta Infant Motor Scale)
- development and cognition (as measured by the Comprehensive Developmental Inventory for Infants and Toddlers in AADC-CU/1601, and the Bayley-3 scale in AADC-010 and AADC-011)
- frequency of and time spent in oculogyric crises
- frequency of floppiness, limb dystonia, stimulus-provoked dystonia and oculogyric facial dyskinesia
- body weight

Comparator effectiveness evidence

3.7 The company explained that none of the clinical trials had a comparator arm because of the ultra-rare nature of AADC deficiency, and for ethical reasons. Instead, the company produced a natural history database (NHDB) of people with AADC deficiency, mainly from published case studies. A total of 163 people were identified who were not involved with any of the company's clinical trials. Of those with sufficient longitudinal data on disease severity, 49 were classified as having a similar phenotype to the trial population. This was AADC deficiency with no or poor head control at 24 months. The motor milestone of each subject was estimated. This was done by assessing the reported evidence related to quantitative motor function (using tools such as PDMS-2 and the Alberta Infant Motor Scale) and qualitative descriptions of individual development. These 49 people with severe AADC deficiency made up the NHDB used in the company's comparative effectiveness analyses. The company explored the possibility of doing an indirect treatment comparison to produce estimates for the comparative effectiveness of eladocagene exuparvovec compared with best supportive care. The company decided that doing a sufficiently robust adjusted indirect treatment comparison using the patient-level data was not feasible. So, a naive analysis was done to estimate the proportion of people who reached motor milestones over 5 years of follow up while having best supportive care. This type of analysis does not adjust for population differences that could potentially bias the results of a comparison between 2 groups of people having different treatment for the same condition. The EAG said that this approach was appropriate. It noted that the alternative matching analyses done by the company predicted people on best supportive care would reach fewer motor milestones than was predicted in the naive analysis. This meant that, while the naive analysis did not adjust for possible prognostic variables, it was a more conservative analysis that favoured best supportive care. The committee concluded that the NHDB provided a suitable source of data for the comparison with eladocagene exuparvovec.

Generalisability

3.8 The issue of generalisability is complicated by the ultra-rare nature of AADC deficiency. The 3 trials comprised about 10% of all people with the condition worldwide. AADC deficiency is most prevalent in Asia (especially Taiwan and Japan). All 3 studies were done in Taiwan, so included a mainly East Asian population. The committee noted that everyone in the trials had the AADC deficiency founder mutation (IVS6+4A>T), which is uncommon in people not from an Asian family background. The company explained that UK clinical experts agree that there is no known correlation between genotype and phenotype in AADC deficiency. Because of this, the clinical experts did not expect there would be differences in outcomes in people from different family background or with different genotypes. Aside from family background and genotype, the clinical experts agreed that the baseline characteristics and demographics in the clinical studies were similar to those of people who would have treatment for AADC deficiency in the UK. The committee concluded that the company's clinical trials were generalisable enough to clinical practice in the NHS for decision making.

Clinical trial results

3.9 The company's evidence submission did not report data beyond 12 months for study AADC-011 and beyond 60 months for studies AADC-CU/1601 and AADC-010. But some further data was provided to the EAG at clarification and technical engagement stages. These were a narrative summary of the long-term efficacy results from a January 2022 data cut, and some additional information on long-term follow up from an ad hoc August 2022 analysis. The company presented results in its evidence submission from a February 2020 data cut of its 3 clinical trials. The results are deemed academic-in-confidence by the company and cannot be reported here. In general, the clinical trial results showed that eladocagene exuparvovec delivered clinically relevant and durable improvements in outcomes. All 28 people in the trials had no motor function at baseline. People having a single dose of eladocagene exuparvovec had substantially improved motor milestones reached compared with baseline. These improvements lasted for at least 5 years. People also had improvements compared with baseline across all secondary outcomes measured in the clinical trials. The committee noted that not all people in the trial had equally rapid or transformative benefits from treatment with eladocagene exuparvovec. It also noted that the long-term efficacy was uncertain because of the small number of people in the trials and the high rate of drop-off at follow-up intervals. The company explained that some people were lost to follow up because of the stringent travel restrictions in Taiwan during the COVID-19 pandemic. Also, longer-term data was not available for all people in the trials at the February 2020 data cut used in the company model. This was because some had not yet reached the first long-term follow-up visit. The EAG said that the additional information provided by the company at the technical engagement stage had confirmed that the reasons for people being lost to follow up were reasonable. It did not think that this showed that there was any risk of selection or attrition bias in the company's results. The committee thought that long-term efficacy of eladocagene exuparvovec was uncertain because of the small number of people in the clinical trials and the high rates of loss to follow up. But it concluded that the results showed the potential for substantial benefits in AADC deficiency.

Natural history database results

3.10 The efficacy data for best supportive care was derived from the company's NHDB comprising 49 people with severe AADC deficiency. The naive analysis of the NHDB suggested that people having best supportive care showed minimal or no improvement in terms of motor milestones reached. No motor milestones were reached in 96% of people over 5 years. In the NHDB, only 2 out of 49 people reached any motor milestone over a 5-year follow-up period. One person was able to walk with assistance and another was able to roll from side to side. Despite it being a naive comparison, efforts were made to ensure that disease severity was comparable between the best supportive care population in the NHDB and those who had eladocagene exuparvovec. The committee concluded that the NHDB provided a sufficient dataset for the comparison of best supportive care with eladocagene exuparvovec.

Economic model

Model structure

3.11 The model structure was informed by the modelling approach adopted in NICE's highly specialised technologies guidance on onasemnogene abeparvovec for spinal muscular atrophy. The company developed a cohort model with 6 health states, 5 of which were based on the motor milestones seen in the 3 clinical trials. These health states progressed from 'worst' to 'best'. They were 'no motor function', 'full head control', 'sitting unassisted', 'standing with support' and 'walking with assistance'. The final state, death, was an absorbing state. The model included a short-term development phase (up to 12 years) and a long-term phase (from 12 years up to lifetime). The short-term development phase used data on the motor milestone reached from all 3 clinical trials for eladocagene exuparvovec, and from the NHDB for best supportive care. In this phase, the company used a 'Bayesian growth model' to predict motor milestone scores up to the end of the 12-year period. The long-term phase assumed that the motor milestones reached were static, and distribution of people between health states was driven by different mortality risk. People were attributed a probability of death in each of these motor milestone health states. These were estimated using survival curves from a study including people with cerebral palsy. A lack of mortality data for people with AADC deficiency meant that cerebral palsy was selected as the most appropriate proxy condition for which robust mortality data was available. The EAG said that, based on its expert clinical advice, it thought that it was appropriate to inform the model using the one accepted for NICE's highly specialised technologies guidance on onasemnogene abeparvovec. This was because of the similarity of motor symptoms between the condition in that evaluation and this one. It added that cerebral palsy is another acceptable proxy condition by which to inform survival estimates for AADC deficiency. The committee concluded that the company's economic model was suitable for decision making.

Motor milestones

3.12 The company explained that the number of people recruited to the 3 clinical trials was relatively small because of the ultra-rare nature of the condition. Also, the number of people contributing outcome data to the economic model at each follow-up time point lessened over time. This was because people entered the clinical trials at different points. So, at the time of the February 2020 data cut used in the company's evidence submission, not everyone had reached all of their follow-up time points. Other people were unable to attend hospital follow-up visits because of restrictions associated with the COVID-19 pandemic. The company said that this attrition in already low patient numbers over time meant that large amounts of missing data had to be imputed for the economic analysis. The EAG agreed with the company that imputation of missing data was appropriate. The company addressed this issue by estimating these missing values using a Bayesian growth model. In the eladocagene exuparvovec arm, observed patient-level total PDMS-2 scores for all 28 people in the 3 clinical trials were used to inform a Bayesian growth model to estimate distribution across the 4 health states. The company fitted a parametric curve (Gompertz) to this observed PDMS-2 data to predict PDMS-2 scores up to 12 years after treatment (the development phase). The company explained that this was preferable to relying only on the observed PDMS-2 data. This was because it accounted for differences in motor milestones reached between people at the time of the data cut by allowing for expected future milestones reached. The company further said that a Bayesian approach was adopted to address issues resulting from a small sample size (n=28), missing data and limited follow up.

Imputing missing data

3.13 The EAG said that the Bayesian model had been implemented correctly and was a reasonable approach for imputing missing data. It said that the company's approach had likely overestimated the effectiveness of eladocagene exuparvovec. This would have favoured the intervention arm compared with best supportive care in the economic analysis. This was because of differences seen between observed and predicted values for each health state. For example, for the 'best' motor milestone state of 'walking with assistance', the predicted estimates were substantially higher than the observed distribution. The EAG explained that it preferred using the observed PDMS-2 data in the economic model without using the Bayesian growth model to predict future motor milestones reached. To impute missing data, the EAG preferred to use a 'last observation carried forward' (LOCF) approach. In this, the value from the previously attended follow-up visit was maintained over time until the next successfully attended follow-up visit. The EAG note that this was a conservative approach. This was because it could suggest maintenance of motor function over time when longer-term data provided by the company at clarification stage showed that some people had reached milestones during that timeframe. The committee accepted the EAG's concerns about the difference between predicted and observed PDMS-2 scores. But it noted that the pooled clinical trial data was difficult to interpret because it was based on very small numbers, high attrition rates and missing data. The committee agreed that the Bayesian growth model might have overestimated the effectiveness of eladocagene exuparvovec. But it thought that the EAG's approach of using the LOCF was unlikely to be clinically plausible. This was because it assumed no motor milestone improvements beyond the last observation for someone lost to follow up. It thought that this would constitute a worst case scenario for eladocagene exuparvovec. The committee concluded that the company's approach of using the Bayesian growth model for predicting PDMS-2 scores was more appropriate for decision making. But it noted the EAG's concerns about the extent of the missing data that were imputed. It agreed that this added substantial uncertainty to the cost-effectiveness estimates because some treatment outcomes were imputed. A patient expert suggested that it might be possible to retrospectively populate some of the imputed data from the people in the trial who were connected to the patient support network for the condition. But the committee thought that the potential validity of such an approach was uncertain. It noted that detailed results for data cuts beyond February 2020 were not available in time for the committee meeting (see section 3.9). It further concluded that it would have been preferable for the company to have used more recent data in its economic model, which would have

Treatment waning in the model

3.14 The clinical experts suggested that AADC deficiency is not a degenerative condition, and that there is no evidence that motor milestones are lost once they have been reached. The company explained that the underlying biology and mechanism of action for eladocagene exuparvovec is such that it durably restores AADC enzyme functioning. It explained that there was evidence of ongoing dopamine production in people 7 years after treatment. It also noted that this same effect has been seen in primate models 15 years after treatment. One clinical expert agreed with the company that there was evidence of increasing levels of dopamine up to 7 years after treatment, and that it might be expected that this would correlate with continuing clinical benefit. The clinical experts agreed that it was clinically plausible that there would be a lasting benefit from treatment over a person's lifetime, but that it was somewhat uncertain. This is because of the insertion of the gene vector into cells of the putamen, a region of the brain, which are known to be non-dividing and durable. The committee concluded that it was plausible that there could be a long-lasting treatment effect over time.

Survival in the model

3.15 The company explained that there was limited published data on mortality in AADC deficiency. To inform survival estimates for people with the condition, the company modelled survival based on motor milestone health states using mortality data from a proxy condition, cerebral palsy. The committee recalled that people with AADC deficiency often die within the first decade of their lives. This premature death is usually from comorbidities such as cardiac events, multiple organ failure, pneumonia, asphyxia, or acute complications during an oculogyric crisis episode, or is unexplained. Because the risk of these comorbidities varies by motor milestone state, it is expected that risk of death also decreases as a person moves up through the motor milestones. The committee understood the lack of mortality data for AADC deficiency was because of its rarity. It concluded that data from cerebral palsy was an acceptable proxy for use in the economic model.

Long-term outcomes

3.16 To inform long-term outcomes, the company first mapped AADC motor milestones to cerebral palsy motor milestones. Survival probabilities of the people with cerebral palsy in each motor milestone health state, taken from a study by Brooks et al. (2014), were reported at 5 time points (10, 15, 20, 25 and 30 years). The company then applied parametric curves to this data to extrapolate survival data for each motor milestone health state in AADC deficiency. For its base case, the company initially selected the log-logistic curve for: 'no motor function', 'full head control', 'sitting unassisted' and 'standing with support', and the exponential curve for 'walking with assistance'. At technical engagement, the company opted for the EAG's choice of Weibull for the first 4 health states. The EAG commented that both log-logistic and Weibull distributions provided a good fit to the observed data from Brooks et al. (2014) for up to 30 years across the motor milestone health states. Weibull provided more conservative survival estimates beyond 30 years, compared with the log-logistic distribution. It agreed with the company's choice of the exponential curve for 'walking with assistance'. But it expressed concern that this overestimated survival of people in this health state. The EAG explained that there was substantial uncertainty in survival extrapolation beyond 30 years. It said that it was unclear whether the use of Weibull for 'walking with assistance' was clinically plausible. This was because it predicted a rate of survival that was very close to that predicted for the 'standing with support' health state beyond 45 years. The clinical experts said that it was quite plausible that survival in 'walking with assistance' health state would be similar to survival in 'standing with support' health state beyond 45 years. They explained that the motor milestone classifications can contain people with different ability levels, and that 'standing with support' represents a very diverse set of people with different severities of AADC deficiency and physical abilities. The committee concluded that the EAG's and company's agreed survival extrapolations were uncertain but appropriate for decision making.

Age and weight in the model

3.17 The company explained that the mean starting age used in the economic model for its base case was 4 years and that the starting weight was 11.1 kg. The company said that these values were the most appropriate because they were derived directly from the mean values in the 3 clinical trials. This aligned directly with the clinical-effectiveness data employed in the model. The committee noted that the EAG's clinical expert had suggested that the baseline characteristics of the clinical trials were generalisable to the UK. The EAG agreed that the age and weight seen in the clinical trials was broadly generalisable. But it said that the expert had noted that children tend to be diagnosed slightly later in the UK than they were in the company's clinical trials in Taiwan, usually between 2 years and 14 years. Because of this, the EAG preferred to use 6 years and 15 kg to more closely match the eligible population in the UK. The weight chosen represents the lowest quantile (0.4^{th} percentile) weight for children aged 6. This was because people with AADC deficiency tend to weigh less than others of the same age because of feeding and digestive problems. The company added that it anticipated earlier identification, diagnosis and treatment of AADC deficiency in the care pathway incorporating eladocagene exuparvovec, as awareness of the benefits of treating it as early as possible increases. Lastly, the company explained that the study by Brooks et al. (2014) used to derive survival estimates from people with cerebral palsy also had a baseline age of 4 years. This meant that survival estimates in the model were also based on a mean age at baseline of 4 years, so the model survival estimates aligned to the trial population. The committee acknowledged that the EAG's preference for age and weight were more closely aligned to the current cohort of people with AADC deficiency having treatment in the UK. But it noted the EAG's scenario analysis that showed this change had a very small effect on the cost-effectiveness results in the economic model. The committee concluded that the company's base-case preference was a better match to the survival data used in the model and was appropriate for decision making.

Utilities in the model

3.18 The company explained that health-related quality-of-life data was not measured in any of the 3 studies. This was because the people included were very young, and had severe cognitive and language impairment, so could not communicate effectively. Also, there was a lack of robust health-related quality-of-life data from preference-based measures in the literature because of how rare AADC deficiency is, particularly in paediatric population. To address this, the company did a series of health-state vignettes. For its base case, it elicited utilities from these vignettes using a time trade-off approach in the general UK population. It also did scenario analyses using the alternative elicitation methods of standard gamble and discrete choice experiment. The EAG said that it agreed with the company's rationale and choice of method for eliciting utilities for the different health states. But it added that, based on clinical expert advice, there was some uncertainty about how well the vignettes linked to each motor milestone reached state to capture the condition. This meant that there was some uncertainty in the utility estimates. The committee noted that the EAG did not consider the company's approach to be inappropriate, but that it had explored 2 alternative sources of utility values. It also noted that the scenario using utility values from NICE's highly specialised technologies guidance on onasemnogene abeparvovec produced an incremental cost-effectiveness ratio (ICER) that was substantially more favourable for eladocagene exuparvovec. It thought that the company's choice of base-case utility values could be considered to be conservative, so concluded that they were appropriate for decision making.

Discount rate for costs and benefits

3.19 In its base case, the company presented cost-effectiveness results assuming a 1.5% discount rate for costs and benefits, rather than 3.5% as used in the NICE reference case. The NICE health technology evaluations manual states that a rate of 1.5% may be considered by the committee if it is satisfied that 3 criteria are met:

- The technology is for people who would otherwise die or have a very severely impaired life.
- It is likely to restore them to full or near-full health.

QALY modifier

3.20 The NICE health technology evaluations manual specifies that a most plausible ICER of below £100,000 per quality-adjusted life year (QALY) gained for a highly specialised technology is normally considered an effective use of NHS resources. For a most plausible ICER above £100,000 per QALY gained, judgements about the acceptability of the highly specialised technology as an effective use of NHS resources must take account of the magnitude of the incremental therapeutic improvement. This is revealed through the number of additional QALYs gained and by applying a QALY modifier. The committee noted that, for this modifier to be applied, there needs to be compelling evidence that the treatment offers substantial QALY gains. It understood that a weight between 1 and 3 can be applied when the QALY gain is between 11 and 29 QALYs. It noted that the modifier is typically calculated by dividing the undiscounted QALY gain by 10, and that it is applied to the QALY in the economic model. The committee concluded it was satisfied a modifier could be applied in line with undiscounted QALY gain. The actual modifier values used in the economic model are confidential and cannot be reported here.

Cost-effectiveness analysis results

3.21 The company and NHS England have agreed a confidential commercial discount. The company considers that all the ICERs from the economic analysis incorporating this discount are commercial in confidence, so they cannot be reported here. From its discussion of the key issues, the committee considered these assumptions to be the most appropriate for decision making:

- a baseline age of 4 years and a weight of 11.1 kg (trial means)
- a discount rate of 3.5% for costs and treatment benefits
- the Bayesian growth model using PDMS-2 scores to predict motor milestone development
- a Weibull curve to extrapolate survival in all health states except for the 'walking with assistance' health state when an exponential curve should be used.

The committee also considered that there was considerable uncertainty associated with the cost-effectiveness analysis of eladocagene exuparvovec because of:

- the low numbers of people in the trials
- the high rate of attrition in follow up over the longer term
- the possibility that using the Bayesian growth model overestimated the effectiveness of eladocagene exuparvovec compared with best supportive care.

The committee noted that the ICER using its preferred assumptions was uncertain. This was largely because the Bayesian growth model possibly overestimated the effectiveness of eladocagene exuparvovec compared with best supportive care. The committee took this uncertainty into account in its decision making. With the QALY modifier included in the economic model (see section 3.20), the committee concluded that eladocagene exuparvovec was sufficiently within the range that NICE considers an effective use of resources for highly specialised technologies. So, eladocagene exuparvovec is recommended for routine commissioning.

Managed access

Consideration of managed access

3.22 The committee considered whether a recommendation with managed access could be an appropriate option for addressing uncertainty in the clinical evidence, and discussed that:

- The company's economic model was structurally robust for decision making but the Bayesian growth model might have overestimated the effectiveness of eladocagene exuparvovec (see section 3.13).
- The key uncertainties related to the immaturity and incompleteness of the motor milestone outcomes data from the company's 3 pivotal trials. This was because people enrolled into the trials at different times, so not everyone had reached all of their follow-up time points at the time of the company's evidence submission. Also, travel disruption caused by the COVID-19 pandemic had led to higher than expected attrition in the numbers of people at follow-up time points (see section 3.12).
- The company's economic model used a February 2020 data cut for its 3 clinical trials, but longer-term data will be available.

  The committee considered that a managed access recommendation would help to address these sources of uncertainty. But it also recognised that the company had taken these uncertainties into account in its value proposition. So, the committee concluded that a positive recommendation for routine commissioning was more appropriate.

Other factors

Equality issues

3.23 No equality issues were identified in this evaluation.

Innovation

3.24 The committee recognised that eladocagene exuparvovec is the first gene replacement therapy for people with AADC deficiency and the first disease-modifying option. So, it agreed that eladocagene exuparvovec is a significant innovation and step-change in the optimal management of AADC deficiency. It thought that the one-time administration of eladocagene exuparvovec will be welcomed by people with AADC deficiency and their carers. It also expected that the treatment will be transformative and life changing for people with the condition, and their families and carers. The committee did not identify additional benefits of eladocagene exuparvovec not captured in the economic modelling.

Conclusion

Recommendation

3.25 The committee took into account its preferred assumptions and the QALY modifier. It considered that the most plausible ICER was uncertain but sufficiently within the range NICE considered an effective use of NHS resources for highly specialised technologies. The committee concluded that eladocagene exuparvovec is recommended for routine use in the NHS for treating AADC deficiency in people 18 months and over with a clinical, molecular and genetically confirmed diagnosis of AADC deficiency with a severe phenotype.

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 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE highly specialised technologies guidance. When a NICE highly specialised technologies guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

4.3 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 AADC deficiency and the doctor responsible for their care thinks that eladocagene exuparvovec 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 and a project manager.

Luke Cowie
Technical lead

Christian Griffiths
Technical adviser

Celia Mayers
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Accreditation