NICE National Institute for Health and Care Excellence

NICE guidance

Etranacogene dezaparvovec for treating moderately severe or severe haemophilia B

Technology appraisal 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.

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

Contents

1 Recommendation

1.1 Etranacogene dezaparvovec is recommended with managed access as an option for treating moderately severe or severe haemophilia B (congenital factor IX [FIX] deficiency) in adults without anti-FIX antibodies. It is only recommended if the conditions in the managed access agreement for etranacogene dezaparvovec are followed.

Why the committee made this recommendation

People with moderately severe or severe haemophilia B without anti-FIX antibodies usually have long-term treatment with FIX concentrates to prevent bleeding episodes (FIX prophylaxis) and on-demand FIX concentrates to stop bleeding during a bleeding episode. A few people with the condition choose to only have on-demand treatment.

Evidence from a clinical trial suggests that the gene therapy etranacogene dezaparvovec reduces the number of bleeding episodes a person has each year. But there is not enough evidence on how well it works in the long term.

An indirect comparison of etranacogene dezaparvovec with FIX prophylaxis suggests that it improves bleeding outcomes. But these results are highly uncertain because of differences in the methods used in the studies and the definition and measurement of bleeding outcomes.

Etranacogene dezaparvovec has the potential to be cost effective compared with FIX prophylaxis. But the cost-effectiveness estimates are highly uncertain because of the uncertainty in how long the treatment effect will last. So, etranacogene dezaparvovec is not recommended for routine use in the NHS.

Collecting more data through a managed access agreement may resolve the uncertainty in the evidence. So, etranacogene dezaparvovec is recommended for use with managed access.

2 Information about etranacogene dezaparvovec

Marketing authorisation indication

2.1 Etranacogene dezaparvovec (Hemgenix, CSL Behring) has a conditional marketing authorisation 'for the treatment of severe and moderately severe haemophilia B (congenital factor IX deficiency) in adult patients without a history of factor IX inhibitors'.

Dosage in the marketing authorisation

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

Price

2.3 The list price per treatment for a single dose of etranacogene dezaparvovec is £2,600,000.

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

3 Committee discussion

The evaluation committee considered evidence submitted by CSL Behring, 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

Details of the condition

3.1 Haemophilia B is an X-linked, congenital bleeding condition characterised by a deficiency of coagulation factor IX (FIX). It mainly affects men, but can affect women in rare cases. The severity of haemophilia B generally correlates with the level of FIX in the blood and is defined as either severe (FIX level below 1%), moderate (FIX level 1% to 5%) or mild (FIX level 5% to less than 40%). Moderately severe haemophilia B does not have a standard definition but is generally considered to be when the FIX level is 1% to 2%. The main symptom of haemophilia is prolonged bleeding but other complications include bleeding into joints and muscles without having had an injury. Patient experts explained that bleeds are not only physically painful but can also have a substantial psychological impact on people with the condition and their family. They often have anxiety or worry about their condition, causing great mental distress. The patient experts explained that FIX prophylaxis treatment for moderately severe or severe haemophilia B (see section 3.2) often requires self-infusion or infusion by carers as often as every 3 to 4 days, which is a substantial treatment burden. They added that this makes planning difficult, especially when travelling, and impairs the ability to be spontaneous. Because of the heavy treatment burden, 1 patient expert described a one-off treatment with etranacogene dezaparvovec, with potential to stop the need for regular FIX prophylaxis, as life-changing. Stakeholders noted that despite having regular prophylaxis treatment, people with severe haemophilia B still have painful bleeds, some of which require lengthy recovery periods, hospital visits and potential hospital stays. Over time these bleeds will lead to joint damage, pain and disability. A one-off treatment with etranacogene dezaparvovec could lead to fewer hospital visits, better joint health and lower rates of disability over time. The committee concluded that moderately

severe or severe haemophilia B substantially affects health-related quality of life.

Treatment pathway and proposed positioning

3.2 The clinical management of haemophilia B usually involves long-term FIX prophylaxis treatment and on-demand treatment with FIX concentrates. FIX prophylaxis treatment involves regular administration of standard half-life FIX concentrates (every 3 to 4 days) or extended half-life FIX concentrates (every 1 to 2 weeks) to prevent bleeding. On-demand treatment includes administration of FIX concentrates at the time of a bleeding episode or before events that may present a higher risk of bleeding. The company noted that, despite being eligible for regular FIX prophylaxis treatment, a small number of people with the condition opt to only have on-demand treatment because of personal choice or clinical challenges. The company proposed that etranacogene dezaparvovec would mainly replace FIX prophylaxis treatment but could also replace on-demand only treatment. The comparators included in the company submission were 4 FIX prophylaxis treatments available on the NHS:

- nonacog alfa (BeneFIX, standard half-life)
- eftrenonacog alfa (Alprolix, extended half-life)
- albutrepenonacog alfa (Idelvion, extended half-life) and
- nonacog beta pegol (Refixia, extended half-life).

The committee concluded that FIX prophylaxis treatment was the most appropriate comparator.

Clinical evidence

The HOPE-B trial

3.3 The primary clinical-effectiveness evidence was from the HOPE-B trial. HOPE-B is an ongoing phase 3, open-label, single-dose, single-arm multinational trial

evaluating etranacogene dezaparvovec in adult males with moderately severe or severe haemophilia B who had routine FIX prophylaxis treatment (n=54). HOPE-B included a lead-in period (minimum 6 months) in which people had FIX prophylaxis treatment. After the lead-in period, people had etranacogene dezaparvovec. Because there was no control arm, outcomes assessed during the lead-in period were compared with outcomes in the post-treatment follow-up period. The company submission presented data up to 24 months after treatment with etranacogene dezaparvovec. At consultation, the company provided additional data for up to 36 months after treatment.

Annualised bleeding rate and change in FIX levels

3.4 The HOPE-B primary outcome is annualised bleeding rate (ABR). Several bleeding outcomes were reported, including various types of bleeds: all bleeds, joint bleeds, spontaneous bleeds and bleeds that needed FIX treatment. At 7 to 24 months after etranacogene dezaparvovec, results showed that:

- the adjusted ABR for all bleeding episodes decreased from 4.19 to 1.51, a reduction of 64% (p=0.0002)
- the adjusted annualised spontaneous bleeding rate decreased from 1.52 to 0.38, a reduction of 75% (p=0.0005)
- the adjusted annualised joint bleeding rate decreased from 2.35 to 0.46, a reduction of 80% (p<0.0001)
- the adjusted ABR for bleeds that needed FIX treatment decreased from 3.65 to 0.99, a reduction of 73% (p=0.0001).

The committee noted that at 7 to 24 months post-treatment, 27 out of 54 people had bleeds (average of 2.7 bleeds per person). It noted that the average number of bleeds after treatment was not substantially different from the lead-in period (average of 3.4 bleeds per person). A clinical expert explained that this may be because people may need a period of relearning in the first couple of years after having etranacogene dezaparvovec, to differentiate between joint pains and bleeds. However, a scan would be needed to confirm whether the pain was because of a bleed. Therefore, it

was possible that people in the trial recorded bleeds in their patient diary when they were actually experiencing joint pain. A key secondary outcome was the change in FIX level between baseline and the post-treatment period. At 24 months post-treatment, the least squares mean increase in endogenous FIX from baseline was 34.13 IU/dl ($p<0.001$). At consultation, the company provided additional follow-up data for 36 months of treatment that continued to show a reduction in bleeding rates (the exact results are confidential so cannot be reported here). The committee concluded that bleeding rates were lower after etranacogene dezaparvovec than during the lead-in period.

Calculation of change in FIX levels

3.5 The EAG highlighted that the company did not report participants' FIX levels during the lead-in period, but instead estimated baseline FIX levels based on their historical haemophilia B severity. This approach meant it was not possible to compare FIX levels during routine prophylaxis treatment in the lead-in period with FIX levels after treatment with etranacogene dezaparvovec. The company said it used this approach because FIX levels would vary depending on the type, brand, dose and frequency of FIX prophylaxis treatment that people were having. It also noted that FIX levels fluctuate after FIX prophylaxis treatment so it would be challenging to identify a representative measurement. It added that a benefit of etranacogene dezaparvovec would be more stable FIX levels because of endogenous production (that is, the body producing its own FIX). The company believed that using a historical estimate of baseline FIX levels instead of actual measurements better represents endogenous FIX production in the lead-in period and leads to a fairer comparison between treatments. The EAG considered that it was not possible to determine how etranacogene dezaparvovec affects FIX levels without comparing FIX levels during FIX prophylaxis with levels after etranacogene dezaparvovec. It added that understanding the change in FIX levels after treatment with etranacogene dezaparvovec would corroborate the other clinical outcomes, and show how etranacogene dezaparvovec reduces bleeds (for example, by increasing FIX levels). A clinical expert said that FIX levels tend to fluctuate after FIX prophylaxis treatment, and that the risk of bleeds is particularly high when FIX levels are low. They added that etranacogene dezaparvovec treatment stabilises FIX levels and so reduces the risk of bleeding

from low FIX levels. The committee considered that a representative measure of people's actual FIX levels during the lead-in period would be useful. But it understood the company's rationale and accepted the company's approach for reporting change in FIX levels. The committee concluded that etranacogene dezaparvovec produces a clinically meaningful increase in endogenous FIX levels.

Magnitude of clinical benefits

3.6 The EAG noted the clinical benefits reported in HOPE-B may have been overestimated. It suggested that reduced physical activity during the COVID-19 pandemic may have meant there were fewer bleeding episodes needing on-demand FIX replacement. The EAG also noted that after the lead-in period, the trial protocol prohibited prophylactic FIX replacement for FIX levels of 5% or more but investigating clinicians could give FIX replacement at their discretion. The EAG considered that clinicians may be less likely to give ad hoc FIX replacement within the trial than in routine practice, to adhere as closely as possible to the preferred study procedures. It considered it plausible that use of FIX replacement would be higher in clinical practice than in HOPE-B. The company highlighted that FIX replacement use remained substantially reduced up to 24 months post-treatment. It suggested that if the COVID-19 pandemic had lowered activity levels, increased activity after the pandemic would have led to more bleeds and increased use of FIX replacement, which was not the case. It also highlighted that the reduction in annualised spontaneous bleeding rates (not related to trauma or activity) from the lead-in period to 7 to 18 months post-treatment, was maintained at 24 months post-treatment. The patient experts shared their experience that activity levels actually increased during the COVID-19 pandemic. Clinical experts added that there was no noticeable difference in reported bleeding episodes during the pandemic. The clinical experts also noted that decisions about giving FIX replacement would be based on normal clinical practice and not influenced by a trial setting. The committee considered it plausible that physical activity (or its intensity) may have increased during the COVID-19 pandemic and recalled that bleeding episodes did not noticeably change during the pandemic. The committee concluded that the COVID-19 pandemic and trial protocol did not have a substantial impact, if any, on the magnitude of clinical benefits reported in HOPE-B.

Indirect treatment comparisons

3.7 Because HOPE-B was a single-arm trial, the company did indirect treatment comparisons to compare the clinical effectiveness of etranacogene dezaparvovec with FIX prophylaxis. The company used the inverse probability of treatment weight method for the comparison with Idelvion because participant-level data was available for both treatments. A matching-adjusted indirect comparison method was used for the comparisons with Alprolix, Refixia and BeneFIX because only summary data was available. The indirect treatment comparisons suggested statistically significant improvements in bleeding outcomes for etranacogene dezaparvovec compared with each of the comparators. The results are considered confidential by the company so cannot be reported here. The EAG believed that the indirect treatment comparisons used the best available methods, but the different methods used in the studies seriously undermined the results of comparisons. The EAG noted that the comparator studies differed from HOPE-B in several important ways, principally relating to analysis populations, outcome definitions and background care. The committee understood the EAG's concerns but acknowledged these limitations related to the quality of the studies rather than the methods used to do the indirect treatment comparisons. The committee concluded that the magnitude of improvement in bleeding outcomes for etranacogene dezaparvovec compared with FIX prophylaxis treatments was uncertain, and it would take this into account in its decision making.

Economic model

Company's modelling approach

3.8 The company presented a cohort-based Markov model. The modelled cohort moved through 4 health states which were based on bleeding events. These were 'no bleed', 'non-joint bleed', 'joint bleed' and 'death', with everyone starting in the 'no bleed' state. Bleeding rates from HOPE-B and the company's indirect treatment comparisons (see section 3.7) were used to calculate transition probabilities between the health states. The committee concluded that the company's model structure was appropriate for decision making.

Comparators in the economic model

3.9 The company modelled treatment with etranacogene dezaparvovec followed by FIX prophylaxis treatment after etranacogene dezaparvovec failure (see section 3.10). The company's model comparison was:

- etranacogene dezaparvovec followed by FIX prophylaxis treatment after etranacogene dezaparvovec failure, compared with
- FIX prophylaxis treatment.

The company presented both a fully incremental analysis (which included 8 treatment combinations) and a pairwise analysis (which included 4 comparisons). The clinical experts explained that in clinical practice, the choice of FIX prophylaxis treatment is based on a variety of factors. This includes the dosing schedule, FIX activity levels, bleeding patterns, mechanism of action and availability of each treatment. A clinical expert said that the most frequently prescribed treatments in clinical practice are extended half-life treatments. This is primarily because they need less-frequent dosing than standard half-life treatments (see section 3.2). At consultation, the company provided an updated pairwise comparison using a basket of comparators weighted by NHS market share. The comparison was:

- etranacogene dezaparvovec followed by a basket of FIX prophylaxis treatments after etranacogene dezaparvovec failure, compared with
- a basket of FIX prophylaxis treatments.

The EAG was concerned that a binary decision between etranacogene dezaparvovec and a basket of alternative treatment options could create misleading conclusions about the cost effectiveness of each treatment strategy and result in the incorrect application of an incremental analysis. The committee noted that some of the alternative treatment options were standard half-life FIX treatments. It was aware that there is declining use of standard half-life treatments in clinical practice. The committee considered that the updated pairwise comparison better reflected treatment choices in clinical practice for moderately severe or severe haemophilia B and reflected the most commonly used comparator according to market share. It concluded using a basket of FIX prophylaxis treatments weighted by NHS

market share was the most appropriate comparator for the economic modelling.

Definition of treatment failure

3.10 The company's economic model included a predicted failure rate of etranacogene dezaparvovec based on extrapolations of observed data from Shah et al. (2022; see section 3.11). The company base case defined treatment failure (that is, the FIX level at which FIX prophylaxis treatment would restart) as a FIX level below 2%, based on advice from 8 NHS clinicians. Once etranacogene dezaparvovec failed, it was assumed that people resumed treatment with 1 of the 4 FIX prophylaxis treatments. The EAG consulted with an NHS clinician who advised that a FIX level of 2% to 5% would be considered as a 'trough' (a minimum level when people are routinely having FIX prophylaxis treatment). They also advised that this level may be too low for people to engage safely in some routine activities such as certain sports. The EAG also noted that people in HOPE-B only stopped FIX prophylaxis treatment when FIX levels were more than 5%. The EAG's base case therefore considered that FIX prophylaxis treatment was more likely to be reintroduced when FIX levels dropped below 5% rather than 2%. The clinical experts explained that restarting FIX prophylaxis treatment is based on many factors, including bleeding symptoms, FIX level and personal preference. One clinical expert said an appropriate definition of treatment failure would be a FIX level between 2% and 3% and another said below 3%. The committee considered that the definition of treatment failure, and when people need to restart FIX prophylaxis treatment, would vary based on several factors, including bleeding symptoms and activity levels. At the first committee meeting, the committee requested that the company should model restarting FIX prophylaxis treatment at a FIX level of 3%. At consultation, the company provided this scenario analysis. The committee concluded that restarting FIX prophylaxis treatment at a FIX level of 3% was appropriate.

Durability of treatment effect

Shah et al. (2022) analysis

3.11 To estimate the long-term durability of etranacogene dezaparvovec treatment the company used analyses by Shah et al. (2022). The analysis combined observed data from HOPE-B (24-month data cut) and AMT-061-01, a phase 2b trial of etranacogene dezaparvovec. At consultation, the company noted that because the results from the 36 months post-treatment data (see section 3.3) were similar, it retained the 24-month data cut in its analyses. Shah et al. (2022) used Bayesian and frequentist linear mixed models to predict FIX levels for up to 25.5 years at an individual and population level. The company also used a supplementary analysis from Shah et al. (2022) which extended to 60 years in its economic model. Both models predicted that no more than 6 out of 55 people (10.9%) would have FIX levels below 2%, up to 25.5 years post-treatment. After the first committee meeting the company updated their analyses to include 2 people from HOPE-B who had initially been excluded from the analyses: 1 person who only had a partial dose because of an adverse reaction and 1 person with a poor response to treatment and a notably high AAV5 (adeno-associated virus 5) neutralising antibody titre. The company preferred to only include the data from the partial dose. The committee noted that the summary of product characteristics for etranacogene dezaparvovec states that high titres of pre-existing neutralising anti-AAV5 antibodies may reduce treatment efficacy but does not state that this is a contraindication to administration. The committee recalled that at the first committee meeting the clinical experts suggested that, in clinical practice, people with a high AAV5 neutralising antibody titre would not have etranacogene dezaparvovec. The committee agreed that people with a high neutralising anti-AAV5 antibody titre should be excluded from the Shah et al. (2022) analysis and this should be reflected in any conditions for use of etranacogene dezaparvovec (see section 3.16). It was understood that although the exact cut-off could differ according to the type of assay used (for example, above 1:678 with a 7-point assay or 1:898 with a 9-point assay), the eligible population would be equivalent irrespective of the assay type used. The committee discussed their concerns with the reported methods used in Shah et al. (2022) and the impact on assumptions about the long-term durability of etranacogene dezaparvovec. The Shah et al. (2022) analyses reported that FIX level measurements were excluded if they were taken up to 5 half-lives

(equivalent to 5 days) after exogenous FIX had been administered. In HOPE-B, exogenous FIX could be used at any time. Further, the committee noted that a key assumption of the durability analyses was that missing data was random. But because investigators would not randomly administer exogenous FIX without taking into account endogenous FIX levels, it considered that this might invalidate the results of the extrapolation. The committee was also concerned about the low participant numbers used to inform the analysis (n=56), and the short follow up of the initial trial data, which was then extrapolated out to 60 years. The EAG noted that the economic model results were highly sensitive to the mean durability estimates (see section 3.12). The committee was also aware that there were other issues with assuming a long-term treatment durability (see section 3.12). The committee concluded that the results of the company's durability analysis were highly uncertain. This was because of issues with the methods used to extrapolate data from a small number of people with a very short follow-up over a long duration. This meant the committee had serious concerns with extrapolations beyond that of the trial data.

Long-term treatment durability

3.12 The company considered that it was plausible that etranacogene dezaparvovec has a long-term treatment effect. This was based on other studies showing that effects of recombinant AAV vector-based gene therapies can be maintained over long periods of time. The most recently published follow-up of a trial for another haemophilia B gene therapy showed stable FIX expression over a period of 8 years (Nathwani et al. 2018). The company noted that in HOPE-B, at 18 months post-treatment, none of the people who expressed endogenous FIX (52 out of 54 people) restarted FIX prophylaxis treatment, and FIX levels remained above 5% in about 95% of people. However, the EAG and committee considered that the extrapolations were highly uncertain because of the small number of people in the analysis and the lack of long-term data (see section 3.11). The committee also discussed 6-year data on AMT-060, an earlier form of etranacogene dezaparvovec (using the same vector and cassette design, but with a wild-type FIX transgene). The company believed that this data showed there is no treatment effectiveness waning for AMT-060, which supports the long-term durability of etranacogene dezaparvovec because the products are similar. The EAG noted that the crude mean FIX activity levels over years 1 to 3 and years 3.5

to 6 may suggest, on the balance of probabilities, a decline in FIX levels. However, the EAG said that neither its nor the company's claim can be demonstrated at conventional levels of statistical significance because of the small sample size (n=9). The EAG understood there are several reasons why gene therapies for haemophilia using an AAV vector may have reduced durability. Evidence from HOPE-B suggested that treatment effect may be reduced in specific subgroups of people who have etranacogene dezaparvovec. These subgroups included people who had corticosteroids to treat transaminase increases, people with pre-existing neutralising anti-AAV5 antibodies, and people with moderate or severe liver steatosis at baseline. The EAG considered it plausible that reduced treatment effect over time may be more likely in these groups. The EAG also noted it received expert advice that suggested that the rate of cell turnover in the areas of the body targeted by etranacogene dezaparvovec, and subsequent illnesses and other treatments that affect these areas of the body or the broader mechanisms of treatment, may lead to reduced efficacy over time. Cells in the liver are responsible for producing FIX. The EAG noted that in HOPE-B people with moderate to severe liver steatosis (baseline steatosis of at least 2) had a reduced treatment effect, but this was inconclusive because of the small sample size. So the EAG considered that further studies would be needed to establish if there was a statistically significant reduction in treatment effect for these groups. The EAG also understood that the liver has a higher rate of cell turnover than other areas of the body. At consultation, the company noted that the existing data for liver-directed recombinant AAV treatments shows durability above the commonly reported lifespan for human hepatocytes. This suggests that either the lifespan of some transduced cells is longer than expected, or that episomes are maintained through some other unknown mechanism. Because of uncertainties in the durability estimates, the EAG carried out a range of scenarios in which duration of effect was truncated over a range of years. The committee noted that shortening the treatment durability profoundly increased the cost-effectiveness estimates. It was mindful that its decision should be based on both the evidence presented and the impact of the evidence on key decision uncertainties. It concluded that the long-term durability of etranacogene dezaparvovec was pivotal to its decision making because it was the main driver of the cost-effectiveness estimates and considered that it was associated with considerable decision uncertainty. It further considered that the AMT-060 sample size was too small to support robust conclusions on the long-term durability of etranacogene dezaparvovec. It also

concluded that longer-term data collection would help to resolve the uncertainty relating to the durability of etranacogene dezaparvovec.

Cost-effectiveness estimates

Difference in probabilistic and deterministic cost-effectiveness results

3.13 The EAG noted that there was a difference between the company's deterministic and probabilistic cost-effectiveness results. The EAG considered the divergence was due to the way health state utilities were modelled. In the company's model, utility values were inputted as independent beta distributions. The EAG considered that modelling best practice should include a baseline and incremental utility to provide to provide a structural correlation between health state utilities. The company clarified it had already included the structural correlation between the health state utilities in its model. Its probabilistic utility values were determined by the lowest value of either the minimum function of the value of the beta distribution of the comparator or etranacogene dezaparvovec. It explained that stakeholders had agreed that quality of life with etranacogene dezaparvovec is superior to that with FIX prophylaxis and on-demand replacement. The EAG considered the company's approach could bias the health state utility estimate of FIX prophylaxis treatment which will always be below that of etranacogene dezaparvovec. The company accepted that the deterministic ICERs should be used for decision making. The committee concluded that the deterministic cost-effectiveness results were the most appropriate.

Cost-effectiveness results

3.14 The committee considered the results of its preferred analysis using:

- treatment failure defined as a FIX level of 3% (see section 3.10)
- a basket of FIX prophylaxis treatments weighted by NHS market share (see section 3.9)

- updated Shah et al. (2022) analysis to include the person who had a partial treatment dose (see section 3.11)
- deterministic cost-effectiveness results (see section 3.13).

  Because etranacogene dezaparvovec and the comparators have confidential commercial arrangements, the exact ICERs are confidential and cannot be reported here. Etranacogene dezaparvovec followed by a basket of FIX prophylaxis treatments after etranacogene dezaparvovec failure had lower costs and higher quality-adjusted life-years (QALYs) than the comparator (a basket of FIX prophylaxis treatments, weighted by NHS market share).

  The committee considered a scenario analysis by the EAG which truncated the durability at each year over the time horizon of the model. This showed that although etranacogene dezaparvovec followed by a basket of FIX prophylaxis treatments was cost effective in the company's base case, the treatment effect would need to persist for a considerable duration beyond the trial data for etranacogene dezaparvovec to remain cost effective (the exact details are confidential and cannot be reported here).

Acceptable ICER

3.15 NICE's manual for health technology evaluations notes that judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the incremental cost-effectiveness ratio (ICER). The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented.

The committee noted concerns around the high level of uncertainty, specifically:

- the results of the indirect treatment comparisons (see section 3.7)
- the Shah et al. (2022) durability extrapolation including the lack of long-term data and methodological challenges in the extrapolation

  Because of the high level of uncertainty in the clinical and economic evidence, the committee was concerned about the limited available trial data.

It was concerned, because of the short trial follow up, that there was insufficient data to reliably conclude on the likelihood of the treatment effect being long enough to achieve cost effectiveness (see section 3.14).

The committee concluded that it could not recommend etranacogene dezaparvovec for routine use in the NHS. This was because although several scenarios varying treatment effect duration resulted in ICERs within the range considered a cost-effective use of NHS resources, the true duration of treatment effect was still highly uncertain and the consequences of decision error would have a significant impact on the NHS. The committee considered that the limited data informing the durability assumptions (see section 3.11) and underpinning the analyses was so uncertain that the plausible ICERs could increase far beyond the acceptable cost-effectiveness range, if the treatment effect waned earlier than the lifetime effect predicted by the company.

Managed access

3.16 Having concluded that etranacogene dezaparvovec could not be recommended for routine use, the committee then considered if it could be recommended with managed access. It recognised that the ongoing HOPE-B trial could provide further high-quality data to address some of the uncertainty about this innovative and complex treatment's long-term durability. The committee considered the company's proposal for ongoing data collection through a managed access agreement, which proposed 5 years of further data collected through:

- the ongoing clinical trial programme
- clinical practice from the National Haemophilia Database and the United Kingdom Haemophilia Centre Doctors Organisation.

The committee recognised that 5 years of additional data collection would not fully resolve the uncertainty around how long etranacogene dezaparvovec remains clinically effective. The committee considered that 5 years of further data in addition to the 36-month trial data would provide a more stable basis on which to extrapolate long-term treatment effectiveness.

The committee also noted that data collected within clinical practice could provide some clarity on the proportion of people that require FIX prophylaxis after etranacogene dezaparvovec (see section 3.11). But the managed access team noted that no meaningful data was likely within a reasonable timeframe. The committee concluded that the details of the company's proposed eligibility criteria in the managed access agreement were suitable. The committee recognised that etranacogene dezaparvovec is a promising treatment with plausible potential for cost effectiveness and concluded that it met the criteria for a recommendation with managed access. It recommended etranacogene dezaparvovec for use with managed access for treating moderately severe or severe haemophilia B in adults without a history of FIX inhibitors. Etranacogene dezaparvovec is recommended only if the conditions in the managed access agreement are followed, including that the person does not have neutralising anti-AAV5 antibodies above a titre of 1:678 (using a 7-point assay) or 1:898 (9-point assay). When the guidance is next reviewed the company should use the committee's preferred assumptions (unless new evidence indicates otherwise), as set out in section 3.14.

Other considerations

Equality

3.17 The committee noted that haemophilia B is rare in women and HOPE-B did not include women. It was aware of clinical advice received by the EAG that the few women who have severe and moderately severe haemophilia B would be affected in the same way as men with the condition. At consultation, the company clarified that its summary of product characteristics states that etranacogene dezaparvovec is not recommended in women of childbearing potential and should not be used during pregnancy or during breastfeeding. Stakeholders also commented that HOPE-B excluded people with uncontrolled HIV and hepatitis, but that this should not exclude them from any recommendation. The committee noted that the summary of product characteristics for etranacogene dezaparvovec does not exclude people with HIV and historical hepatitis B and C. But, that the safety and efficacy of etranacogene dezaparvovec has not been

established in people with acute or uncontrolled chronic hepatitis infections. The committee concluded that any recommendation would not exclude people with HIV or hepatitis, and would not need to differentiate between men and women.

Uncaptured benefits

3.18 The committee also noted benefits of etranacogene dezaparvovec that were not included in the economic model. The company noted that etranacogene dezaparvovec has the potential to reduce long-term joint damage because it reduces bleeding episodes which are associated with joint damage. The company also noted that etranacogene dezaparvovec might lower mortality, which could lead to higher QALY benefit. The committee noted that the effect of etranacogene dezaparvovec on mortality has not been shown. The committee agreed to take the possibility of uncaptured benefit into its decision-making but concluded that this did not have a material effect because of the committee's considerable concerns about the uncertainty in the long-term durability estimates.

Conclusion

3.19 The committee noted that etranacogene dezaparvovec is a promising treatment that could substantially improve the lives of people with severe or moderately severe haemophilia B. The committee concluded that etranacogene dezaparvovec could not be recommended for routine use in the NHS. This was because of the considerable uncertainty in long-term treatment durability assumptions. The committee was satisfied that further data collection through a managed access arrangement could gather further evidence on treatment effectiveness to provide longer-term data that would improve the robustness of the extrapolations. It recommended etranacogene dezaparvovec for use with managed access for treating severe or moderately severe haemophilia B in adults without a history of FIX inhibitors. It is recommended only if the conditions of the managed access agreement are followed.

4 Implementation

4.1 When NICE recommends a treatment as an option for use with managed access, NHS England will make it available according to the conditions in the managed access agreement. This means that, if a patient has moderately severe or severe haemophilia B and the healthcare professional responsible for their care thinks that etranacogene dezaparvovec is the right treatment, it should be available for use, in line with NICE's recommendations and the criteria in the managed access agreement. Further information can be found in the Innovative Medicines Fund principles.

4.2 Interim funding for etranacogene dezaparvovec will be available through the Innovative Medicines Fund when positive final draft guidance is released.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance when the drug or treatment, or other technology, is approved for use with managed access. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, for use with managed access, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance or agreement of a managed access agreement by the NHS in Wales, whichever is the later.

5 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

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

Megan John
Chair, technology appraisal committee D

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.

Dilan Savani and Victoria Gillis-Elliott
Technical leads

Victoria Kelly
Technical adviser

Kate Moore and Celia Mayers
Project managers

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