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SMC2649

etranacogene dezaparvovec concentrate for solution for infusion (Hemgenix®)

CSL Behring UK Limited

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The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the orphan medicine process

etranacogene dezaparvovec (Hemgenix®) is accepted for use within NHSScotland on an interim basis subject to ongoing evaluation and future reassessment.

Indication under review: for the treatment of severe and moderately severe haemophilia B (congenital factor IX deficiency) in adult patients without a history of factor IX inhibitors.

In an open-label, non-randomised, single-arm, phase III study, the annualised bleeding rate was reduced following treatment with etranacogene dezaparvovec compared with a lead-in period of regular factor IX prophylaxis.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Etranacogene dezaparvovec is an advanced therapy medicinal product. It is a gene therapy that employs a non-replicating, recombinant adeno-associated virus-based vector serotype 5 (AAV5) containing a codon-optimised coding DNA sequence for the human coagulation factor IX variant R338L (FIX-Padua) under the control of a liver-specific promoter (LP1). It is designed to introduce a copy of the human factor IX coding DNA sequence, synthesised from vector-transduced liver tissue, into hepatocytes to achieve prolonged expression of active human factor IX in the plasma and address the root cause of haemophilia B. The recommended dose of etranacogene dezaparvovec is a single intravenous infusion of 2 x 10^{13} genome copies/kg bodyweight.[1, 2]

1.2. Disease background

Haemophilia B is a rare, inherited bleeding disorder which is due to a partial or complete deficiency in factor IX resulting in increased risk of bleeding. It is linked to a mutation in the factor IX gene on the X-chromosome and occurs almost exclusively in males; females are mainly carriers. The severity of the condition depends on the level of factor IX in the plasma and haemophilia B has been defined as mild when factor IX levels are 5% to 40% of normal (approximately a third of cases); moderate when 1% to 5% of normal (approximately a third of cases) and severe when <1% of normal (approximately a third of cases).[2] There is no standard definition for moderately severe disease but the company submission suggests that factor IX levels ≤2% of normal has been used in clinical trials for gene therapy for moderately severe or severe disease.

Prolonged bleeding is the main symptom associated with haemophilia B and it can occur following injury or for no reason (that is spontaneous bleeding). Bleeding can occur into muscles or joints, most often knees, elbows and ankles which can lead to swollen and damaged joints. Recurrent bleeding into joints causes synovial proliferation and inflammation which can lead to end-stage degeneration (haemophilic arthropathy). The resulting pain and limited movement can affect ability to participate in daily activities including school or work and sport. Living with haemophilia B can have a negative impact on well-being and impair quality of life.[2]

1.3. Treatment pathway and relevant comparators

Factor IX replacement is either administered in response to a bleed (on demand) or regularly to prevent bleeding (prophylaxis). Prophylactic therapy with standard half-life factor IX products requires infusion every few days while extended half-life factor IX products allow administration every 1 to 2 weeks. Current guidelines recommend that all children with severe haemophilia B should receive primary prophylaxis and all children with factor IX levels of 1 to 3% should be considered for primary prophylaxis. Prophylaxis should be offered to patients who have had at least one spontaneous joint bleed or have established joint damage due to haemarthroses and have ongoing bleeding. Therefore, the majority of adult patients with severe or moderately severe haemophilia B would have been receiving factor IX prophylaxis from childhood. Treatment is not curative and peaks and troughs in plasma factor IX levels may result in breakthrough bleeding episodes. Patients require regular intravenous infusions and are at risk of associated complications of infection and thromboses from the use of indwelling catheters. These factors can lead to poor adherence which can contribute to failure of prophylaxis. The development of neutralising antibodies against the replacement factor IX may also limit efficacy.[2, 3]

The relevant comparators are recombinant factor IX products given as prophylaxis including albutrepenonacog alfa (Idelvion®), eftrenonacog alfa (Alprolix®), nonacog alfa (BeneFIX®) and nonacog beta pegol (Refixia®).

1.4. Category for decision-making process

Eligibility for interim acceptance decision option

Etranacogene dezaparvovec has conditional marketing authorisation from the Medicines and Healthcare Products Regulatory Agency.

Eligibility for a PACE meeting

Etranacogene dezaparvovec meets SMC orphan criteria.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the use of etranacogene dezaparvovec comes from the open-label, single-arm, phase III study, HOPE-B.

Table 2.1. Overview of relevant studies[2, 4]

Criteria	HOPE-B
Study design	Open-label, single-arm, non-randomised, phase III study comprising a 4-week screening period, a lead-in period of ≥26 weeks, a treatment plus post-treatment follow-up period to 18 months and a long-term follow-up period to 5 years.
Eligible patients	• male patients aged ≥18 years with inherited haemophilia B which was severe or moderately severe (plasma factor IX activity of <1% or 1% to 2% respectively). • no history of use of factor IX inhibitors • receiving continuous routine factor IX prophylaxis • had received >150 previous exposure days of treatment with factor IX and had been on stable prophylaxis for ≥2 months before screening.
Treatments	Eligible patients received continuous factor IX prophylaxis for ≥26 weeks during the lead-in period, followed by a washout of ≥3 days for standard half-life products and ≥10 days for extended half-life products to ensure trough level of endogenous factor IX activity. Patients then received a single intravenous infusion of etranacogene dezaparvovec 2 x 10^{13} genome copies per kg.
Randomisation	Not applicable.
Primary outcome	ABR, comparing the rate during the 52 weeks after stable factor IX expression (7 to 18 months post-dose) with the rate during the lead-in period.
Secondary outcomes hierarchically tested	• Endogenous factor IX activity at 6 months, 12 months and 18 months post-dose. • Annualised use of factor IX replacement therapy during months 7 to 18 post-dose. • Annualised infusion rate of factor IX replacement therapy during months 7 to 18 post-dose. • Percentage of patients with trough factor IX activity <12% of normal during months 7 to 18 post-dose compared with lead-in period. • ABR comparison between etranacogene dezaparvovec and prophylaxis for **superiority** during months 7 to 18 post-dose compared with lead-in period. • Rate of spontaneous bleeding events during months 7 to 18 post-dose compared with lead-in period. • Rate of joint bleeding events during months 7 to 18 post-dose compared with lead-in period.

	• iPAQ score (total physical activity score) during 12 months post-dose compared with the lead-in period. • EQ-5D-5L VAS score during 12 months post-dose compared with the lead-in period.
Statistical analysis	The study primarily assessed the non-inferiority of ABR during months 7 to 18 post etranacogene dezaparvovec compared with the lead-in period using a non-inferiority at a margin of 1.8; superiority was assessed as a secondary outcome. A hierarchical statistical testing strategy was applied for the primary and secondary outcomes in the order listed above with no formal testing of outcomes after the first non-significant outcome in the hierarchy. Analyses were performed in the FAS which included all patients who entered the lead-in, received etranacogene dezaparvovec and had at least one post-treatment efficacy assessment.

ABR = annualised bleeding rate; EQ-5D-5L = EuroQol 5-Dimension 5-Level; FAS = full analysis set; iPAQ = International Physical Activity Questionnaire VAS = visual analogue scale

The HOPE-B study is ongoing with the primary analysis results published 18 months post etranacogene dezaparvovec treatment; results for updated analyses at 24- and 36-months post-treatment are also available. At the primary analysis, the upper boundary of the 95% confidence interval (CI) for the difference between the post etranacogene dezaparvovec treatment period and the lead-in period was less than the pre-specified non-inferiority margin of 1.8, and non-inferiority was considered demonstrated. Superiority was subsequently assessed and demonstrated as one of the secondary outcomes at 18 months post etranacogene dezaparvovec treatment. Factor IX activity increased from a baseline pre-treatment with etranacogene dezaparvovec of 1.2% to 39% at 6 months, 41% at 12 months and 37% at 18 months.[2, 4, 5] Details of available results assessed at 18 months, and the latest 36-month post-treatment analyses are presented in Table 2.2.

Table 2.2. Results for the primary and selected secondary outcomes assessed in the FAS of HOPE-B[2, 4, 6-8]

	Factor IX lead-in period (n=54)	**Months 7 to 18 post etranacogene dezaparvovec (n=54)**		**Months 7 to 36 post etranacogene dezaparvovec (n=52)**	
		Result	**Difference/ratio versus lead-in (95% CI)**	**Result**	**Difference/ratio versus lead-in (95% CI)**
Primary outcome: ABR (all bleeding episodes)					
Cumulative number of episodes	136	54	N/A	N/A	N/A
ABR	4.19	1.51	Rate ratio 0.36 (0.20 to 0.64) p<0.001	1.52	Rate ratio 0.36

Secondary outcomes					
Annualised use of factor IX replacement therapy (IU/year)	257,339	8399 (7 to 12 months) 8487 (13 to 18 months)	-248,825 (-291,150 to -206,500), p<0.001	-	-246,763
Annualised infusion rate of factor IX replacement therapy (infusions/year)	72.5	2.5	Rate ratio 0.03 (0.01 to 0.10) p<0.001	2.6	*
Percentage of patients with trough factor IX activity <12% of normal	80%	6.0%	Odds ratio 0.036 (0.014 to 0.093), p<0.001	-	-
ABR for spontaneous bleeding episodes	1.52	0.44	Rate ratio 0.29 (0.12 to 0.71), p=0.003	*	*
ABR for joint bleeding episodes	2.35	0.51	Rate ratio 0.22 (0.10 to 0.46), p<0.001	*	*

ABR = annualised bleeding rate; CI = confidence interval; FAS = full analysis set; IU = international units

**a number of results at the 7 to 36 month post etranacogene dezaparvovec analysis were considered confidential by the company.*

*Other data were also assessed but remain confidential.**

An additional secondary outcome, not included in the hierarchical testing, was the percentage of patients who remained free from routine factor IX prophylaxis post etranacogene dezaparvovec. At the time of the primary analysis, 96% (52/54) of patients had discontinued factor IX prophylaxis; one patient received 10% of the dose of etranacogene dezaparvovec and one patient had very high baseline AAV5 neutralising antibodies. At 36 months post etranacogene dezaparvovec, 94% (51/54) of patients remained free of continuous factor IX prophylaxis; including one additional patient who returned to using factor IX prophylaxis after AAV5 decline to 2 to 5% and return of bleeding phenotype at 30 months post etranacogene dezaparvovec.[2, 4, 6]

After etranacogene dezaparvovec treatment, 63% (34/54) of patients had no bleeding episodes during the 7 to 18 months post-treatment period compared with 26% (14/54) during the lead-in period.[2]

There was also a reduction in the adjusted ABR for bleeds that required treatment with factor IX from 3.65 during the lead-in period to 0.84 during 7 to 18 months post etranacogene dezaparvovec; rate ratio 0.23 (95% CI 0.12 to 0.46).[1]

2.2. Health-related quality of life outcomes

In HOPE-B, the International Physical Activity Questionnaire (iPAQ) total physical activity score and the EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) visual analogue scale (VAS) were assessed as secondary outcomes in the hierarchical testing. Results for iPAQ were not significantly different

between the lead-in period and the etranacogene dezaparvovec 12-month post-dose period; LS mean difference -721.2 (-1771 to 328). Results for EQ-5D-5L VAS were also similar (80.9 in lead-in and 81.0 following treatment) but were not formally tested. Descriptive results at the updated 36-month follow-up were also similar to the lead-in period.[2, 8]

The disease specific assessment, Haemophilia Specific Quality of Life Index (Haem-A-QoL; range 0 to 100, with higher scores indicating poorer quality of life) which covers 10 domains, was an exploratory outcome in HOPE-B. There were numerical improvements in the total score and several individual domains (treatment, feelings, future and work or school) 12 months after etranacogene dezaparvovec treatment compared with the lead-in.[2, 4]

There were small improvements in the exploratory outcome of Patient-Reported Outcomes, Burdens and Experiences (PROBE) questionnaire summary score between the lead-in and post-treatment periods. There were minimal or no improvements observed for additional exploratory outcomes of Work Productivity and Activity Impairment (WPAI) Questionnaire, Brief Pain Inventory (BPI) and Haemophilia Activities List (HAL).[2]

2.3. Supportive studies

CM-AMT-061-01 is an ongoing open-label, single-arm, phase IIb study in three patients with severe or moderately severe haemophilia B who received etranacogene dezaparvovec 2 x 10^{13} genome copies/kg. The primary outcome was factor IX activity 6 weeks after dosing which ranged from 24% to 38%. The study is ongoing with follow-up to 5 years to assess longer-term efficacy and safety.[2]

2.4. Indirect evidence to support clinical and cost-effectiveness comparisons

The submitting company presented separate, pair-wise, unanchored indirect treatment comparisons (ITCs) of etranacogene dezaparvovec (using data from the HOPE-B study)[8] with prophylactic recombinant factor IX treatments as follows:

- inverse probability of treatment weighting (IPTW) versus albutrepenonacog alfa (Idelvion®), using data from the PROLONG-9FP study (n=40 eligible patients).[9]
- matching-adjusted indirect comparison (MAIC) versus eftrenonacog alfa (Alprolix®), using data from the B-LONG study (n=32 from primary population and n=61 from secondary population).[10]
- MAIC versus nonacog beta pegol (Refixia®), using data from the Paradigm 2 study (n=17 from primary population and n=29 from secondary population).[11]
- MAIC versus nonacog alfa (BeneFix®), using data from the NCT00093171 study (n=17 eligible patients).[12] However this MAIC was not used to inform the economic model; instead a HOPE-B pre-post analysis was conducted in the 19 patients who received BeneFix® during the lead-in.

A number of efficacy outcomes were compared but those used in the economic analysis were ABR and annualised joint bleeding rate (AjBR).

Table 2.3: Summary of indirect treatment comparisons of etranacogene dezaparvovec versus each comparator[13]

Comparator	Comparison type	ABR (RR, 95% CI)	AjBR (RR, 95% CI)
Idelvion®	Adjusted (IPTW)	0.19 (0.09 to 0.41), p=<0.001	0.09 (0.03 to 0.25), p=<0.001
Alprolix®: primary population	Adjusted (MAIC)	0.14 (0.08 to 0.25), p=<0.001	N/A
Alprolix®: secondary population	Adjusted (MAIC)	0.19 (0.08 to 0.44), p=0.0001	0.15 (0.03 to 0.65), p=0.0111
Refixia®: primary population	Adjusted (MAIC)	0.24 (0.07 to 0.82), p=0.0231	N/A
Refixia®: secondary population	Adjusted (MAIC)	0.30 (0.10 to 0.94), p=0.0395	N/A
BeneFIX®	Pre-post analysis of HOPE-B	*	*

ABR=annualised bleeding rate; AjBR = annualised joint bleeding rate; CI = confidence interval; IPTW = inverse probability of treatment weighting; MAIC = matching-adjusted indirect comparison

**results for the indirect comparison of etranacogene dezaparvovec versus BeneFIX® were considered confidential by the company.*

*Other data were also assessed but remain confidential.**

3. Summary of Safety Evidence

Safety data have been published for the safety population of HOPE-B (all patients who received etranacogene dezaparvovec, n=54) to 24-months post-treatment. Any adverse event (AE) was reported by 69% (37/54) of patients during the 6-month lead-in period and by all 54 patients during the post etranacogene dezaparvovec treatment period, 70% of which were treatment-related. Serious treatment emergent AEs were reported in 26% of patients. One patient (1.9%) discontinued due to a treatment emergent AE.[2, 5]

The most frequently reported AEs of any grade in the 24-month post-treatment period were: arthralgia (35%), headache (30%), nasopharyngitis (28%), fatigue (26%), increased ALT (20%), COVID-19 (19%), back pain (17%), pain in extremity (17%), increased AST (15%) and increased blood creatine phosphokinase (15%).[2, 5]

Infusion-related reactions (including urticaria, eye pruritus, flushing, dizziness and pyrexia) were reported by seven patients (13%).[1, 2, 4]

Due to the potential risk of hepatotoxicity, the SPC recommends that liver transaminases, liver ultrasound and elastography are performed before treatment with etranacogene dezaparvovec. Following treatment, liver transaminases should be monitored weekly for ≥3 months and if ALT is elevated, the SPC recommends management including a course of prednisolone. The SPC provides recommendations for continued ALT and factor IX monitoring every 3 months from month 4 to 1 year, every 6 months during year 2 and then yearly.[1]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- Etranacogene dezaparvovec is the first gene therapy for the treatment of haemophilia B which addresses the underlying cause of the disease. This may reduce the burden of the disease on patients, avoiding the need for regular infusions and reduced the risk of infection, thrombosis and breakthrough bleeding.[2]
- Evidence from the HOPE-B study, primarily assessed 7 to 18 months post-dose, has demonstrated that etranacogene dezaparvovec was associated with a reduction in ABR (non-inferior and superior) compared with regular factor IX prophylaxis during the lead-in period. This was considered clinically relevant. Updated results have shown that the treatment effect is maintained to 3 years [2, 4, 6, 8]
- The reduction in ABR is supported by results for secondary outcomes including a reduction in joint bleeds (from 59% during lead-in to 20% at 18 months) and an increase in the patients experiencing no bleeds (from 26% to 63%). In addition, almost all patients, 96% to 18 months and 94% to 36 months, were able to stop regular factor IX prophylaxis.[2, 4, 6]

4.2. Key uncertainties

- The key evidence from the HOPE-B study comes from a small number of patients, n=54. The study results are limited by the non-randomised, single-arm, open-label design which may introduce potential bias. The study was single-arm but the use of the lead-in period allowed comparison of outcomes post-treatment with etranacogene dezaparvovec with previous prophylactic factor IX treatment, with patients acting as their own controls.[2, 4]
- Etranacogene dezaparvovec is administered as a single infusion which is not repeated. The primary analysis of HOPE-B was performed 18 months after treatment. Updated results are available to 36 months which generally suggest that the treatment effect is maintained but durability of effect beyond 3 years currently remains uncertain. The efficacy is anticipated to be long-lasting but further follow-up is awaited to confirm the long-term efficacy and safety of etranacogene dezaparvovec for haemophilia B.[2, 4, 6]
- The secondary outcomes of factor IX levels at 6, 12 and 18 months post etranacogene dezaparvovec could not be compared with corresponding levels during the lead-in period since these had not been recorded. Estimated baseline factor IX levels were used instead. [2, 4]
- The reduction in bleeding during HOPE-B was not associated with notable improvements in any of the quality of life measurements assessed. This may have been affected by the lack of suitably sensitive assessment tools and the demanding monitoring schedule initially after etranacogene dezaparvovec treatment.[2, 4]
- The study did not exclude patients based on pre-existing AAV5 neutralising antibody, but the SPC cautions that a titre above 1:678 may impede transgene expression. In HOPE-B, one patient had very high AAV5 neutralising antibody titres (1:3212) and showed no factor IX expression or response to etranacogene dezaparvovec. Additional analyses were presented with results excluding this outlying patient. At baseline, AAV5 neutralising antibody titres up to 1:678.2 were found in 20 patients, while the remaining 33 patients were negative. There was a numerically lower mean factor IX activity reported in patients with pre-existing neutralising

anti-AAV5 antibodies but there was no clinically meaningful correlation found between patients` pre-existing anti-AAV5 antibody titre and their factor IX activity at 18 months post-dose. The treatment effect of etranacogene dezaparvovec regardless of AAV5 neutralising antibodies will be further investigated as part of the conditional marketing authorisation.[1, 2, 4]

- There are no comparative data for etranacogene dezaparvovec and the company has performed ITCs versus prophylactic treatment with recombinant factor IX products.[13] The results indicate that etranacogene dezaparvovec was associated with significantly lower ABR and AjBR compared with these products. However, due to the limited available data, there are a number of limitations which affect the robustness of these results.

4.3. GB conditional marketing authorisation specific obligations

The MHRA specific obligations notes that in order to confirm the efficacy and safety of etranacogene dezaparvovec in adult patients with severe and moderately severe haemophilia B (congenital factor IX deficiency) without a history of factor IX inhibitors, the company should submit:

1. the final results including 5 years follow-up of the pivotal phase IIb study (CT-AMT-061-01) by 30 June 2024.
2. the final results (5 years of data) of pivotal HOPE-B study with 54 patients by 31 October 2025.
3. irrespective of baseline anti-AAV5 neutralising antibody titre, the 1-year follow-up interim analysis report after the first 50 patients are enrolled in study CSL222-4001 (an observational post-authorisation long-term study to characterise the safety and effectiveness (up to 15 years) of etranacogene dezaparvovec in patients with haemophilia B by 31 December 2026.[14]

The MHRA specific obligations may address some of the uncertainties in the longer-term clinical evidence presented, including further evidence relating to the durability of treatment effect up to 5 years, however beyond this, it is likely to remain uncertain.

4.4. Clinical expert input

Clinical experts consulted by SMC considered that etranacogene dezaparvovec potentially fills an unmet need in this therapeutic area by removing the need for regular factor IX prophylaxis. They considered that it is a therapeutic advancement by stabilising factor IX levels.

4.5. Service implications

The extremely high upfront acquisition cost for this single-dose treatment is likely to have significant service implications and is associated with financial risk to the service if the long-term predicted clinical benefits do not materialise.

The availability of etranacogene dezaparvovec may reduce the need for regular factor IX infusions but may have service implications for liver monitoring.

5. Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of **etranacogene dezaparvovec**, as an orphan medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Haemophilia B is a congenital, life-long, bleeding disorder caused by reduced levels of factor IX. In patients with severe or moderately severe disease, factor IX levels are generally considered low enough to lead to recurrent bleeding in daily life making prophylactic factor IX treatment appropriate. Patients often experience frequent bleeds, particularly into joints which can result in chronic pain, long-term joint damage and arthropathy. There is also the risk of catastrophic intracranial bleeds. Patients may live in fear of triggering a bleeding episode and the psychological and physical burden of the disease, the progressive damage to joints and the burden of treatment have a substantial negative impact on the quality of life and mental well-being of patients, families and carers.
- Currently there is no cure for haemophilia B and available treatment generally relies on weekly injections of prophylactic factor IX. However, there are significant fluctuations in factor IX levels between doses of prophylaxis resulting in a constantly varying risk of bleeding. A small proportion of patients have difficulties with venous access and need central venous access, with associated risks of infection and thrombosis, or forgo prophylaxis.
- As a one-off treatment, etranacogene dezaparvovec is the first licensed treatment for adults with severe and moderately severe haemophilia B and addresses an unmet need by providing constant, steady state levels of factor IX. Patients are generally no longer dependent on regular prophylactic factor IX to remain protected against bleeding and are free from the concerns around a missed dose.
- The availability of etranacogene dezaparvovec may provide consistently higher factor IX levels than prophylactic treatment. This in turn may reduce bleeding episodes and so reduce progression of haemarthropathy, reducing the impact of haemophilia B on long-term disability and the need for interventions such as joint-replacement surgery. Etranacogene dezaparvovec may eliminate the burden of regular injections. It provides a useful alternative for patients who have problems with venous access.
- An improved control of factor IX levels may relieve the psychological burden of haemophilia B and allow patients to lead a more normal life, engaging in activities including education, work, family and social events. It may reduce the anxiety for patients and their families over managing the condition and the constant need to plan activities around factor IX level fluctuations. This would be expected to be a significant additional benefit and allow patients to perform normal daily tasks that others take for granted for example gardening, wearing a new pair of shoes, or visiting the dentist.

- The availability of etranacogene dezaparvovec may have service implications related to the initial assessment of patient suitability for an irreversible treatment and the close monitoring in the months following treatment. However, these are expected to lessen in subsequent years.

Additional Patient and Carer Involvement

We received a patient group submission from Haemophilia Scotland, which is a Scottish charitable incorporated organisation. Haemophilia Scotland has received 42% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from Haemophilia Scotland participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The economic case is outlined below in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis.
Time horizon	The model had a lifetime time horizon of 83 years.
Population	Full licensed indication (i.e. adults with severe and moderately severe haemophilia B)
Comparators	The weighted comparator is a "basket" comparator taking the average cost and effect values of the four factor IX replacement therapies according to their respective market share in clinical practice. These were: • Alprolix® (etrenonacog alfa) • BeneFIX® (nonacog alfa) • Idelvion® (albutrepenonacog alfa) • Refixia® (nonacog beta pegol)
Model description	A Markov cohort model was developed and consisted of four health states; 'no bleed', 'bleed (joint)', 'bleed (not joint') and 'death'. All patients entered the model at age 18 in the 'no bleed' health state.
Clinical data	Clinical inputs for etranacogene dezaparvovec were informed by the HOPE-B study, an ongoing, open-label, single-arm, non-randomised, phase III study which evaluated the efficacy and safety of etranacogene dezaparvovec in 54 patients with haemophilia B. Clinical inputs for the comparators were informed through an ITC.
Extrapolation	The submitting company used the methods outlined in Shah et al. (2022) for extrapolating durability of treatment effect of etranacogene dezaparvovec. This source used data from Bayesian and frequentist linear mixed modelling approaches which were used to predict long-term factor IX activity levels over a 60-year time horizon. The results of these predictions informed the proportion of patients who remained free from the need for prophylaxis at any point in time. Data from the 36-month data cut from HOPE-B were used as the primary data to inform the extrapolations (n=55).
Quality of life	EQ-5D-5L data were collected during the HOPE-B study at baseline, 6-months (lead-in final), 12 months and 36 months post-treatment points. The submitting company used the van Hout et al. (2012) mapping function to transform translate the EQ-5D-5L values to EQ-5D-3L values. Adverse event disutilities were also included.

Costs and resource use	Medicine costs included were acquisition costs, administration costs and adverse event costs. Other costs included were follow-up costs, disease management costs and event-related costs and disease monitoring costs.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.

6.2. Results

In the base case, etranacogene dezaparvovec (with PAS) dominated the weighted comparator meaning it was estimated as having lower costs and greater health outcomes than the comparator (based on their list prices). The biggest driver of results were the reduced costs in the etranacogene dezaparvovec arm with the QALY gain coming from a reduced rate of bleed events.

6.3. Sensitivity analyses

Descriptions of key scenario analyses are presented below in Table 6.3.1. The results (with PAS), which cannot be presented here for confidentiality reasons, showed that reducing the time horizon to 5 years and capping the treatment durability for etranacogene dezaparvovec at 6 years had significant impacts on the ICER, highlighting the uncertainty of the long-term modelled effects with the treatment.

Table 6.3.1 Sensitivity and Scenario Analysis Results

	Parameter	**Base case**	**Scenario**
	Base case		
1	Durability of etranacogene dezaparvovec	Capped at 60 years	Capped at 6 years
2	Time horizon	83 years	5 years
3	Time horizon	83 years	10 years
4	Model starting age	18	42 (HOPE-B mean age)
5	Utility values	Treatment-specific	Health state-specific

6.4. Key strengths

- The model type chosen was suitable.

6.5. Key uncertainties

- The extrapolation of the treatment effect of etranacogene dezaparvovec was modelled for a 60 year time horizon based on 36 months of data, which leads to a high degree of uncertainty. The length of treatment effect was shown to have a large impact on the ICER in the sensitivity analysis.
- Due to the culmination of potential biases, small sample sizes and poor overlap between studies the ITC is associated with limitations, as noted above. This introduces a large degree of uncertainty in the economic results which were based on the ITC.
- The clinical evidence from HOPE-B came from a single-arm trial with few participants. Patients were also asked to note key outcomes used in the economic model, such as

bleeding rates, in diaries, meaning that clinical inputs are uncertain.

- The calculations of the annualised bleeding rates (ABR) were used as transition probabilities but were based on uncertain data and in some cases very small cohorts of patients.
- Treatment-specific utilities were applied in the model. Sensitivity analysis showed that the predicted QALY gains were sensitive to using health state specific values.

*Other data were also assessed but remain confidential.**

7. Conclusion

The Committee considered the benefits of etranacogene dezaparvovec in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as etranacogene dezaparvovec is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted etranacogene dezaparvovec for use on an interim basis in NHSScotland.

8. Guidelines and Protocols

The British Society of Haematology published "Guidelines on the use of prophylactic factor replacement for children and adults with haemophilia A and B" in May 2020.[2]

International consensus recommendations on the management of people with haemophilia B was published in April 2022.[15]

The World Federation of Hemophilia (WFH) published guidelines for the management of hemophilia, 3rd Edition in 2020.[16]

9. Additional Information

9.1. Product availability date

July 2024

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per treatment (£)
etranacogene dezaparvovec	**2 x 10^{13} genome copies/kg as a single infusion**	**2,600,000**

Costs from the company submission. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 1 patient estimated to receive treatment in year 1 rising to 3 patients in year 5. SMC clinical expert responses indicate the uptake rate may be higher than this.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 17 May 2024.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.