NICE National Institute for Health and Care Excellence

NICE guidance

Efanesoctocog alfa for treating and preventing bleeding episodes in haemophilia A in people 2 years and over

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.

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.

Contents

1 Recommendations

1.1 Efanesoctocog alfa is recommended as an option for treating and preventing bleeding episodes in people 2 years and over with haemophilia A (congenital factor VIII deficiency), only if:

- they have a factor VIII activity level of less than 1% (severe haemophilia A)
- the company provides it according to the commercial arrangement.

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

Why the committee made these recommendations

For this evaluation, efanesoctocog alfa was only considered for people with severe haemophilia A, in line with the evidence provided by the company. This does not include everyone who it is licensed for.

Current treatment options for severe haemophilia A include ongoing treatment with factor VIII replacement therapies (including standard half-life and extended half-life therapies) or emicizumab to prevent bleeding. On-demand factor VIII replacement therapies are used to treat bleeding.

The results from a clinical trial suggest that there may be fewer bleeding episodes with ongoing efanesoctocog than with previous ongoing factor VIII replacement therapy, but this is uncertain. There is limited clinical-effectiveness evidence directly comparing efanesoctocog alfa with currently available treatments for severe haemophilia A, and there are substantial limitations with the available indirect comparisons. So, it is uncertain how well efanesoctocog alfa works compared with other haemophilia A treatments.

Because of uncertainties in the clinical-effectiveness evidence and the economic model,

the cost-effectiveness estimates are uncertain. But, when considering all the available evidence and economic analyses, efanesoctocog alfa is a cost-effective use of NHS resources. So, it is recommended.

2 Information about efanesoctocog alfa

Marketing authorisation indication

2.1 Efanesoctocog alfa (Altuvoct, Swedish Orphan Biovitrum) is indicated for 'treatment and prophylaxis of bleeding in patients 2 years and above with severe or moderate haemophilia A (≤ 5% endogenous plasma factor VIII activity).'

Dosage in the marketing authorisation

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

Price

2.3 The list price per vial of 1,000 IU efanesoctocog alfa is £2,400 (£2.40 per IU; company submission). It is available as 250 IU, 500 IU, 750 IU, 1,000 IU, 2,000 IU, 3,000 IU and 4,000 IU vials.

2.4 The company has a commercial arrangement. This makes efanesoctocog alfa 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 Swedish Orphan Biovitrum, 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 committee meetings were held before the marketing authorisation for efanesoctocog alfa from the Medicines and Healthcare products Regulatory Agency was granted. The committee considered evidence for using efanesoctocog alfa for people of all ages. The final marketing authorisation is restricted to people 2 years and over.

The condition

Details of the condition

3.1 Haemophilia A is caused by a gene mutation that results in the inability or reduced ability to produce functional factor VIII, which is vital in stable blood clot formation. This leads to prolonged bleeding after injury and, when severe, bleeding into joints and muscles without any injury. Haemophilia A is an inherited condition that mostly occurs in men and boys. Women and girls who carry the haemophilia gene may have mild or, rarely, moderate to severe symptoms of bleeding. For this evaluation, the company only presented clinical- and cost-effectiveness evidence for efanesoctocog alfa in severe haemophilia A (see section 3.2). The clinical experts explained that severe haemophilia A usually presents in the first few years of life with joint or muscle bleeds. Occasionally, it may cause spontaneous and potentially fatal bleeds in any tissue. The clinical experts explained that subclinical bleeds are also associated with the condition. These bleeds can cause chronic pain and joint damage, potentially affecting mobility and, over time, needing surgery. The patient experts highlighted that the risk of bleeding can limit jobs, sports and other activities. It also has a substantial psychological effect on people with the condition and affects the quality of life of carers of children with the condition. Also, because haemophilia A is inherited, there may be several siblings with the condition in the same family, increasing its impact on carers. The committee recognised that severe haemophilia A is a chronic condition that significantly affects the lives of people affected by it.

Population

3.2 The licence for efanesoctocog alfa includes people 2 years and over with moderate or severe haemophilia A. The company submission included people of all ages, but the committee can only make recommendations within the marketing authorisation. The company submission only included people with severe haemophilia A. The severity of haemophilia A is classed according to the amount of clotting factor remaining compared with expected levels. Mild haemophilia is defined as over 5% of normal clotting factor, moderate as between 1% and 5%, and severe as less than 1%. The company explained that it had excluded people with moderate haemophilia A from its decision problem because there was no evidence for efanesoctocog alfa in this population. Also, it did not expect efanesoctocog alfa to be routinely used in people with moderate haemophilia A. The clinical experts explained that, generally, treatment for severe haemophilia A differs from that for mild and moderate forms (see section 3.3). But some people with moderate haemophilia A and factor VIII activity levels between 1% and 2% would be offered the same treatments as people with the severe form. They added that healthcare professionals would be keen to use efanesoctocog alfa in these people. The committee considered this but concluded that it had not been presented with clinical- and cost-effectiveness evidence for people with moderate haemophilia A. Also, it thought that differences in the treatment pathway meant that it was likely that the clinical- and cost-effectiveness outcomes would differ between people with severe and moderate haemophilia A. So, it was unable to make recommendations for using efanesoctocog alfa in moderate haemophilia A.

Clinical management

Treatment pathway

3.3 The clinical experts explained that the main aim of treatment for severe haemophilia A is to prevent bleeding and resulting long-term damage, especially to joints. This is through prophylaxis to prevent bleeds, and on-demand treatment for bleeding episodes when needed. The available treatment options for long-term prophylaxis are:

- Factor VIII replacement therapy to replenish missing clotting factor in the blood through an intravenous injection: standard and extended half-life factor VIII replacement therapies are available.
  - The standard half-life (SHL) factor VIII replacement therapies available for prophylaxis in the NHS (all used every 2 to 3 days) are:
    - octocog alfa
    - simoctocog alfa
    - moroctocog alfa
    - turoctocog alfa.
  - The extended half-life (EHL) factor VIII replacement therapies available for prophylaxis in the NHS are:
    - efmoroctocog alfa, every 3 to 5 days
    - turoctocog alfa pegol, every 4 days, for people 12 years and over.
- A non-factor VIII treatment, emicizumab, is also recommended for people of all ages in NHS England's clinical commissioning policy for emicizumab as prophylaxis for people with congenital haemophilia A without factor VIII inhibitors. Emicizumab is a monoclonal antibody administered subcutaneously every 1 to 4 weeks and mimics the activity of factor VIII to restore clotting function.

  For people who have bleeds on prophylaxis, additional doses of factor VIII replacement therapy (known as on-demand treatment) can be used. People having factor VIII replacement therapy will use extra doses of the same treatment that they are using as prophylaxis. People having emicizumab will need to have some SHL or EHL available to use for on-demand treatment of bleeds. The company presented evidence for efanesoctocog alfa separately for people who had not had treatment (from now on, 'previously untreated people' or PUPs) and people who had had treatment (from now on, 'previously treated people' or PTPs). The clinical experts explained that guidelines recommend starting prophylaxis at the first joint bleed. But they added that some treatment centres may use emicizumab before this, often

from the first few weeks of life. So, PUPs are all very young children. The marketing authorisation for efanesoctocog alfa is in people 2 years and over. The committee was aware that most people with severe haemophilia A will have treatment before age 2 years, so noted that most people who are eligible for efanesoctocog alfa will be PTPs. But the committee thought that PUPs who start treatment aged 2 years or over would be eligible for efanesoctocog alfa. The committee concluded that the treatment for severe haemophilia A includes prophylaxis with factor VIII replacement therapy or emicizumab. Extra on-demand factor VIII replacement therapy is used for bleeds.

Limitations of current treatment options

3.4 The clinical and patient experts highlighted that current treatment options do not always prevent bleeding episodes and are associated with administration challenges. Frequent factor VIII replacement injections can damage veins, resulting in pain on administration and increasing the chance of 'vein collapse'. The frequency of injections is especially challenging in older people and young children, who often have poor venous access. It can reduce adherence to and eventually prevent the use of prophylactic factor VIII replacement therapies, leading to poor bleed control. Young children often need a central venous access device, which needs placing surgically and has an infection risk. The patient experts highlighted the potential stigma associated with visible bruising from frequent intravenous injections. They also explained that the volume and frequency of factor VIII replacement injections needed can make travelling a challenge. It can also be hard to plan injections around daily life. Also, up to 30% of people with severe haemophilia A develop antibodies to factor VIII (called inhibitors). This makes treatment with clotting factor replacement less effective. In NHS practice, most people with haemophilia A have emicizumab, which is given subcutaneously, rather than intravenous factor VIII replacement therapies. The committee noted that most people having emicizumab in HAVEN-3 had no bleeding events. But the patient and clinical experts highlighted that some people choose not to have emicizumab for reasons including:

- There is uncertainty about the level of bleed coverage with emicizumab compared with factor VIII replacement therapies. The patient experts

described that they know that they have the highest bleed coverage immediately after having factor VIII replacement therapy, so can plan higher risk activities then. This is not possible when having emicizumab.

- It is not a factor VIII replacement therapy, so factor VIII activity levels are not monitored with a blood test. This means that it is difficult to find out the level of protection from bleeding.
- It cannot be used as an on-demand treatment, so people need further factor VIII replacement injections for individual bleeding episodes. These can be hard to manage, especially in young children who may need hospitalisation if they are not used to intravenous injections.
- People who contracted hepatitis C from contaminated factor VIII blood products had subcutaneous treatment for the hepatitis C, so may find this administration route traumatic.

The patient experts highlighted that their goal is to have a 'haemophilia free mindset'. But this is not possible with current treatment options because of frequent dosing schedules and the risk of bleeds on prophylaxis. The clinical experts highlighted that it is uncertain whether factor VIII replacement therapies or emicizumab better control bleeding. But some healthcare professionals consider that emicizumab may be associated with a lower rate of bleeds than currently used factor VIII replacement therapies. The patient experts explained that preventing bleeds was an important factor to them when considering a treatment option. But they would also consider the method of administration of a treatment. This meant they would welcome a less demanding administration schedule to allow for normal daily activities. So, the choice to have factor VIII replacement therapies or emicizumab is multifactorial and varies among people with severe haemophilia A. The committee noted that efanesoctocog alfa is administered weekly because it has a longer half-life than other factor VIII replacement therapies. It also noted that it can be used for both on-demand treatment and prophylaxis. The committee concluded that a new treatment option with effective bleeding control and a less frequent dosing schedule would be welcomed by people with haemophilia A.

Proposed positioning and comparators

Relevant comparators in PUPs

3.5 The comparator listed in the NICE scope for efanesoctocog alfa is established clinical management, including:

- factor VIII replacement therapy (prophylaxis and on demand)
- emicizumab.

In its original submission, the company's decision problem included the following comparators for PUPs:

- efmoroctocog alfa (prophylaxis with on-demand treatment), which is the only EHL factor VIII replacement therapy licensed for people under 12 years
- emicizumab (prophylaxis), with an SHL factor VIII replacement therapy, octocog alfa (on demand).

At the first committee meeting, the clinical experts explained that there is variation in the preferred treatment for people newly diagnosed with haemophilia A. They noted that some people start having emicizumab from diagnosis. Other people start having factor VIII replacement therapies, including both SHL and EHL factor VIII replacement therapies. At consultation, the company maintained that its initial comparators were the most appropriate. But it provided a scenario analysis comparing efanesoctocog alfa with an SHL, simoctocog alfa. This was based on clinical opinion that:

- simoctocog alfa is perceived to have a low risk of inhibitor development
- SHLs are only used in PUPs when there is a high risk of developing inhibitors or a central nervous system bleed at diagnosis.

The clinical experts highlighted that use of SHLs in PUPs is low and expected to decrease over time. This is because of the considerable treatment burden and reduced bleeding control compared with emicizumab and EHL factor VIII replacement therapies. They highlighted data from the UK National

Haemophilia Database from people with factor VIII activity levels less than 1% with no inhibitors, who had prophylactic treatment during 2023. The data showed that 7% of people under 12 years had prophylactic SHLs (octocog alfa, simoctocog alfa, turoctocog alfa or moroctocog alfa) in the NHS. The committee noted that SHL use is decreasing, but thought that it is still used in NHS clinical practice. So, the committee concluded that emicizumab, SHL factor VIII replacement therapies (octocog alfa, simoctocog alfa, turoctocog alfa or moroctocog alfa) and efmoroctocog alfa were all relevant comparators in PUPs.

Relevant comparators in PTPs

3.6 The committee next considered the relevant comparators for efanesoctocog alfa in PTPs. In its initial submission, the only comparator considered by the company for PTPs was emicizumab (prophylaxis), with an SHL factor VIII replacement therapy, octocog alfa (on demand). At consultation, the company repeated that it thought that emicizumab was the only appropriate comparator for efanesoctocog alfa in PTPs. But it updated its base case to include the EHLs available in the NHS for PTPs (efmoroctocog alfa and turoctocog alfa pegol). The committee noted that turoctocog alfa pegol was not licensed in people under 12 years, so would not be available for some PTPs. The company also provided a scenario analysis comparing efanesoctocog alfa with a weighted basket of SHLs (simoctocog alfa, moroctocog alfa, turoctocog alfa and octocog alfa).

At the second meeting, the committee noted that the UK Haemophilia Centre Doctors' Organisation (UKHCDO) data indicated that 12% of people 12 years and over with severe haemophilia A have SHLs in NHS clinical practice. It considered whether these people would swap to efanesoctocog alfa if available. The patient expert expected that, if efanesoctocog alfa were available, most people would be keen to have weekly administration. But they highlighted that some older people who started treatment with SHLs may not want to change treatment. This is because of fears about treatment switching after using contaminated factor VIII products. Also, the limited reduction in injection frequency when changing from SHLs (3 times weekly) to the current EHLs (twice weekly) may not be appealing enough for people adept at self-injecting to swap. But the patient experts noted that the further reduction in administration frequency with efanesoctocog alfa

may mean that some people will switch from SHLs to efanesoctocog alfa. So, the committee agreed that SHLs were a relevant comparator in PTPs and considered a basket of all available SHLs in its preferred analysis after consultation. The committee recalled that the decision to use emicizumab or factor VIII replacement therapies is individual and based on many different factors (see section 3.2). So, efanesoctocog alfa will likely be considered for people who would otherwise have emicizumab or factor VIII replacement therapies. The committee agreed that the relevant comparators in PTPs were emicizumab, SHL (octocog alfa, simoctocog alfa, turoctocog alfa or moroctocog alfa) and EHL (efmoroctocog alfa or turoctocog alfa pegol) factor VIII replacement therapies.

Clinical evidence

Data sources

3.7 The clinical evidence for efanesoctocog alfa came from XTEND-1, a phase 3, open-label, non-randomised trial. XTEND-1 enrolled PTPs 12 years and over with severe haemophilia A and no inhibitors to factor VIII. It had 2 arms:

- Arm A enrolled 133 people who had had a prophylaxis regimen with factor VIII replacement therapy or emicizumab for at least 6 months in the last year. People could not have had emicizumab within 20 weeks of screening. People in arm A had 50 IU/kg efanesoctocog alfa weekly for 52 weeks.
- Arm B enrolled 26 people who had had on-demand SHL or EHL factor VIII replacement therapies and had a history of 1 or more bleeds per month over the past 6 or 12 months. People in arm B had efanesoctocog alfa 50 IU/kg on demand for the first 26 weeks, then switched to weekly efanesoctocog alfa prophylaxis for another 26 weeks.

  The primary outcome in XTEND-1 was the mean annualised bleeding rate (ABR) at 52 weeks. A key secondary outcome was an intrapatient comparison of ABR for the efanesoctocog alfa arm A with a prospective observational study 242HA201/OBS16221 before starting efanesoctocog alfa. The comparison used data from 78 people who had had a minimum 6 months of prophylaxis treatment with EHL or SHL factor VIII replacement therapy in the

prospective observational study before they enrolled in arm A of XTEND-1. The company also presented data from XTEND-Kids, a single-arm study in which 74 PTPs under 12 years had a once-weekly prophylactic dose of 50 IU/kg of efanesoctocog alfa for 52 weeks. The clinical experts agreed that XTEND-1 outcomes were aligned with other haemophilia A trials in severe populations. But they noted untreated bleeds are hard to measure because they rely on patient reporting. The committee noted several limitations with the XTEND-1 trial design:

- There was no control arm comparing efanesoctocog alfa with standard care (other factor VIII replacement therapies or emicizumab).
- There was no randomisation between on-demand and prophylactic efanesoctocog alfa for people having on-demand therapy when they entered the study.
- People could not have had emicizumab within 20 weeks of screening, so very few people in the trial had previously had emicizumab.
- There is a high risk of bias when using intrapatient comparisons instead of comparing with a control arm:
  - Observed changes may be because of the improved monitoring and treatment from being in a clinical trial. For example, there is improved adherence to treatment in a clinical trial compared with in an observational study.
  - Some people would have improvement in bleeding rates over time regardless of treatment (regression to the mean), which could be wrongly thought to be a treatment effect. The committee noted that people in XTEND-1 had high bleeding rates at baseline, so improvement in bleeding rate could have been because of regression to the mean, rather than the treatment effect of efanesoctocog alfa.

    The committee concluded that the relevant evidence for efanesoctocog alfa came from the XTEND-1 and XTEND-Kids trials. But it noted the limitations in the XTEND-1 trial design.

Trial results

3.8 The results of XTEND-1 suggested that:

- People having prophylaxis with efanesoctocog alfa had a reduction in ABR from baseline (prior prophylaxis). For people in arm A, the mean ABR for treated bleeds reduced from 3.20 at baseline to 0.71 (95% confidence interval [CI] 0.52 to 0.97) after 52 weeks. The upper limit of the one-sided 97.5% confidence interval was less than the company's prespecified value, denoting a clinically meaningful treatment effect.
- People having on-demand treatment with efanesoctocog alfa had a reduction in ABR from baseline (prior on-demand treatment). For people in arm B, the ABR for treated bleeds reduced from 35.70 at baseline to 21.42 after 26 weeks (standard deviation [SD] 7.41). After people switched to efanesoctocog alfa weekly prophylaxis for the last 26 weeks of XTEND-1 the ABR for treated bleeds was 0.69 (SD 1.35).
- Similar improvements in bleeding rate were seen when considering any bleeds, regardless of whether the bleed was treated (exact results are confidential and cannot be reported here).
- Weekly prophylaxis with efanesoctocog alfa reduced the risk of bleeding compared with prestudy SHL and EHL factor VIII replacement therapy prophylaxis in an intrapatient comparison in people who participated in both arm A of XTEND-1 and the prospective observational study (difference in mean ABR for treated bleeds -2.27, 95% CI -3.44 to -1.10; $p<0.0001$).
- While having weekly efanesoctocog alfa prophylaxis, 65% of arm A had no bleeds after 52 weeks of prophylaxis and 77% of arm B had no bleeds after 26 weeks of prophylaxis. Everyone in arm B had at least 1 bleed during the 26 weeks they had on-demand treatment.
- Factor VIII activity levels after weekly injections were maintained at week 26 in people having prophylaxis, suggesting a maintained response to treatment. Similar postinjection factor VIII activity levels were seen in the on-demand and prophylaxis arms.
- Improvements in baseline were seen for Haem-A-QoL Physical Health and EQ-5D scores.

The committee noted that similar results had been reported for bleeding outcomes in XTEND-Kids. The committee recalled the limitations with the design of XTEND-1 (see section 3.7). It concluded that the clinical trial results suggested efanesoctocog alfa may be clinically effective at preventing bleeds for PTPs with severe haemophilia A. But it thought that this was associated with uncertainty.

Generalisability

3.9 The licence for efanesoctocog alfa includes people 2 years and over with moderate or severe haemophilia A. The EAG highlighted that the population in XTEND-1 was narrower than the licence for efanesoctocog alfa because it excluded:

- people with moderate haemophilia A
- people under 12 years
- PUPs
- people with inhibitors to factor VIII.

The committee recalled that the company had positioned efanesoctocog alfa for people with severe haemophilia A. So, it could only make recommendations within this population (see section 3.2). It noted that there was data available from XTEND-Kids for PTPs under 12 years. The clinical experts highlighted that they would want to use efanesoctocog alfa for people under 12 years. This is because the convenience of weekly dosing would reduce the burden on families. Also, maintained factor VIII activity levels would allow children to take part in games and sports with a reduced risk of bleed. The committee noted similar bleeding outcomes and pharmacokinetic data from XTEND-Kids to that of XTEND-1. It agreed that the XTEND-1 results were likely generalisable to people under 12 years. The committee acknowledged that there was no clinical evidence to inform efanesoctocog alfa's treatment effect in PUPs or people with inhibitors to factor VIII. The clinical experts explained that there was no biological reason

for the treatment effect to differ based on whether people had previous treatment. So, they explained that data from PTPs was likely generalisable to PUPs. The committee also noted that, because efanesoctocog alfa was a factor VIII replacement therapy, it would have limited effectiveness in people with inhibitors. This would mean that healthcare professionals were unlikely to use it in this population. So, the committee did not consider it necessary to exclude people with inhibitors from its recommendation. It was concerned that most people in the NHS have emicizumab (see section 3.4), but XTEND-1 trial excluded people who had had emicizumab within the last 6 months. So, the trial provided no information on the potential effect on adherence and bleeding rates of switching from subcutaneous emicizumab to intravenous efanesoctocog alfa. The committee concluded that there was no evidence available for efanesoctocog alfa in PUPs, and that this increased uncertainty in decision making in this population. Given the clinical expert advice, it agreed that the results of XTEND-1 were likely to be generalisable to people under 12 years and PUPs. But it noted that the prior therapies used in the trial were not reflective of NHS practice.

Comparative clinical effectiveness

Company's ITC with emicizumab before consultation

3.10 There were no trials directly comparing efanesoctocog alfa with emicizumab, so the company did an indirect treatment comparison (ITC) to establish the relative efficacy. The clinical-effectiveness data for emicizumab came from HAVEN-3. This was an open-label study in 152 PTPs 12 years and over with severe haemophilia A and no inhibitors. It had 4 arms:

- People who had had on-demand regimens were randomised to have prophylaxis with 1.5 mg/kg emicizumab weekly (arm A), 3 mg/kg every 2 weeks (arm B) or no prophylaxis (arm C).
- People who had had prophylaxis regimens had 1.5 mg/kg emicizumab weekly (arm D).

The company did not have access to individual patient data from HAVEN-3,

so it did a matching-adjusted indirect comparison (MAIC) to derive relative effectiveness. The company said that an unanchored MAIC was needed because there was no common comparator across XTEND-1 and HAVEN-3. So, it adjusted the XTEND-1 population to balance covariates with aggregate patient data from HAVEN-3. It presented several analyses in its original submission, including analyses varying the arms of HAVEN-3 and XTEND-1 used for matching or pooling data from across all arms of each trial. At the first meeting, the committee concluded that the company's MAIC was unlikely to provide reliable estimates of relative clinical effectiveness between treatments because:

- People in HAVEN-3 had a higher bleeding rate at study entry than people in XTEND-1. The committee noted that this suggested that the HAVEN-3 population had more severe disease or the measurement of bleeds differed across trials. Baseline bleeding rate was likely a prognostic factor that had not been adjusted for in the company's MAIC.
- There was inconsistency in the company's matched covariates and outcomes depending on the arms used in the analysis.
- There were small sample sizes after matching with the company's preferred arms at the first committee meeting (arm B of HAVEN-3 and arm B of XTEND-1, which included people who had had an on-demand regimen, chosen to align with use of 2-weekly emicizumab).

  At the first meeting, the results of the MAIC using the company's preferred arms suggested that efanesoctocog alfa reduced the bleeding rate when compared with emicizumab. The incidence rate ratio (IRR) ABR for any bleed was 0.28 (95% CI 0.10 to 0.81) and for any treated bleed was 0.47 (95% CI 0.15 to 1.44). The committee concluded that the company's MAIC comparing emicizumab with efanesoctocog alfa had significant limitations and thought that the results were very uncertain.

Company's ITC with efmoroctocog alfa before consultation

3.11 There were no trials directly comparing efanesoctocog alfa with efmoroctocog alfa. The clinical-effectiveness data for efmoroctocog alfa came from the A-LONG

trial. This was an open-label study with 3 arms in 165 PTPs 12 years and over with severe haemophilia A and no inhibitors:

- People who had had prophylaxis entered arm 1, in which the dose of efmoroctocog alfa was increased over time from 25 to 65 IU/kg.
- People who had had on-demand therapy could enter arm 1 or be randomised to arm 2 (weekly 65 IU/kg efmoroctocog alfa) or arm 3 (on-demand therapy with 10 to 50 IU/kg efmoroctocog alfa).

  The company said that there was no common comparator in XTEND-1 and A-LONG. Because the company had individual patient data available from A-LONG, in its original submission, it used a propensity score-matching (PSM) approach for the ITC. In this, it weighted individual data from each trial (pooling all arms) to balance baseline characteristics. Compared with efmoroctocog alfa, efanesoctocog alfa reduced the bleeding rate for all outcomes (IRR ABR for any treated bleed 0.29, 95% CI 0.17 to 0.51). At the first meeting, the committee acknowledged that a PSM approach is normally preferred when individual patient data is available. But it was concerned that the company's approach to ITCs for efmoroctocog alfa and emicizumab adjusted the XTEND-1 data to different populations, and that these populations were likely not comparable. The committee noted that the ABR for any bleed was not recorded in A-LONG, so this outcome could not be included in the ITC. The committee also noted that, when applied in the model, the results suggested that people having emicizumab had a higher bleeding rate than efmoroctocog alfa. This did not align with data from the HAVEN-3 prestudy. So, the committee agreed that the results of the company's original ITC approach lacked face validity.

Company's ITC with efmoroctocog alfa, emicizumab and other EHLs after consultation

3.12 After consultation, the company updated its base case to use a consistent ITC approach for efmoroctocog alfa and emicizumab. It submitted a MAIC that adjusted both the A-LONG and XTEND-1 trial populations to the aggregate data from HAVEN-3 in a MAIC (that is, adjusting to the same population for all 3 trials). This used the committee's and EAG's preferred arms at the first committee

meeting. These were the prophylactic arms of HAVEN-3 (arm D) and XTEND-1 (arm A), and the pooled arms of A-LONG. The company's and EAG's base cases included an adjustment for baseline bleeding rate and a scenario that excluded this. The MAIC also adjusted for age, weight, race and presence of target joints. The committee noted the inherent uncertainty in unanchored MAICs. This was because they assumed that all prognostic variables and effect modifiers had been accounted for in the adjustment. It also noted the differences in baseline characteristics between XTEND-1, HAVEN-3 and A-LONG. It agreed that the company's updated base-case MAIC, including adjustment for baseline ABR, was helpful because it adjusted to the same trial population (HAVEN-3). The outcomes of this ITC are considered commercial in confidence by the company so cannot be reported here.

After consultation, turoctocog alfa pegol was also included in the company's and EAG's base cases as a comparator. The company assumed the same effectiveness for both efmoroctocog alfa and turoctocog alfa pegol. The committee concluded that treatment effect for efanesoctocog alfa compared with efmoroctocog alfa and emicizumab was uncertain. It reiterated that a PSM approach is normally preferred when individual patient data is available (see section 3.11). But, it recalled that only aggregate data was available for emicizumab from HAVEN-3. It agreed that, in this case, it was preferable to adjust the trial data to the same population for all comparators. So, it considered the MAIC, adjusting the XTEND-1 and A-LONG trial populations to that in HAVEN-3 and including adjustment for baseline ABR, in its decision making.

Intrapatient comparisons of prestudy compared with on-study efanesoctocog alfa in XTEND-1

3.13 At the first committee meeting, the committee noted that the XTEND-1 prestudy included people having factor VIII replacement therapies. So, by comparing the prestudy and on-study bleeding rates, there was direct evidence to inform the clinical effectiveness for efanesoctocog alfa prophylaxis compared with factor VIII replacement therapies. The company highlighted that the prestudy in XTEND-1 included a mixture of people having SHLs and EHLs. It said that the treatment effect was expected to differ by half-life. So, it did subgroup analyses by EHL or SHL use in the XTEND-1 prestudy. The prior SHL subgroup was used to inform

the relative effectiveness for SHLs, assuming that all SHLs had the same efficacy. The exact results are considered commercial in confidence by the company and so cannot be reported here. The committee thought that the prestudy compared with on-study intrapatient comparison was useful for informing the comparative clinical effectiveness of SHLs.

Committee preferences for incorporating comparative clinical-effectiveness evidence into the economic modelling

3.14 At the second committee meeting, the committee considered the methodology and results of the following approaches that were provided by the company:

- the PSM comparing efanesoctocog alfa with efmoroctocog alfa (see section 3.11)
- the unanchored MAIC comparing efanesoctocog alfa with efmoroctocog alfa and emicizumab in which XTEND-1 and A-LONG population data was adjusted to aggregate data from HAVEN-3 (see section 3.12)
- intrapatient comparisons of prestudy compared with on-study data from XTEND-1 to compare efanesoctocog alfa with:
  - prestudy SHL factor VIII prophylaxis
  - prestudy EHL factor VIII prophylaxis (see section 3.13)
- the anchored MAIC comparing efanesoctocog alfa with emicizumab, in which the prestudy populations were used as a common comparator (see the committee papers for further information).

  At the first committee meeting, the committee also requested that the company provide an analysis using the on-demand arms in each trial as an anchor. The company did not provide this. The committee noted that there were substantial limitations and uncertainties with all potential approaches. The committee considered the results of the MAICs and the subsequent economic model results when these were incorporated into the model. It noted that most results were relatively consistent. It acknowledged that the lack of controlled trials in haemophilia A made generating comparative

evidence extremely challenging. It also acknowledged that haemophilia A is a rare disease. Its preferred approach, given those available, was to use the MAIC adjusting the XTEND-1 and A-LONG trial populations to that in HAVEN-3. This incorporated comparative clinical effectiveness for efmoroctocog alfa and other EHL factor VIII treatments and emicizumab into the model. This was because it allowed consistency between approaches for various comparators. It thought that the company's and EAG's approach of using the prestudy compared with on-study intrapatient comparison was acceptable for informing the comparative clinical effectiveness of SHLs in the model. But the committee concluded that its preferred approach was associated with limitations and uncertainties, and that this made the results uncertain.

Economic model

Company's economic model

3.15 The company developed a 3-state Markov model to determine the cost effectiveness of efanesoctocog alfa. The health states were 'no bleeds', 'any bleeds' and 'death'. All people entered the model in the 'no bleeds' health state, after which a proportion were assumed to have a bleed each cycle. Some of these bleeds were treated with extra, on-demand factor VIII replacement injections, and others were untreated. All bleeds were associated with a short-term (7-day) and long-term (6-month) utility decrement, and treated bleeds accrued an extra cost. The company also modelled a utility decrement for the proportion of people assumed to have factor VIII activity levels below 20%. The cycle length was 6 months with a half-cycle correction and a lifetime time horizon. A proportion of people transitioned to death each cycle, aligned with general population mortality. That is, no mortality benefit was assumed for efanesoctocog alfa, and people with haemophilia A were assumed to have same mortality as the general population. The EAG commented that the model may have missed the granularity in bleeding severities and locations, but it expected this to have a limited impact on the results. The committee concluded that the company's general model structure was simplistic but may be acceptable for decision making.

Company's modelling of factor VIII replacement therapies

3.16 The company assumed equal effectiveness for efmoroctocog alfa and turoctocog alfa pegol, and for all SHLs included in its model. For costs, the company modelled factor VIII replacement therapies differently in PUPs and PTPs:

- PUPs:
  - SHLs: assumption that 100% have simoctocog alfa (see section 3.5)
  - EHLs: 100% have efmoroctocog alfa (only EHL licensed in people under 12 years)
- PTPs:
  - SHLs: weighted basket of available SHLs in the NHS (octocog alfa, simoctocog alfa, moroctocog alfa and turoctocog alfa), in which the usage data was informed by the UKHCDO annual report (2023)
  - EHLs: included comparisons with efmoroctocog alfa and turoctocog alfa pegol in the base case, and provided a scenario including a basket of EHLs, assuming that 50% have efmoroctocog alfa and 50% have turoctocog alfa pegol.

    At consultation, 1 clinical expert provided market share UKHCDO data in people with severe haemophilia A with no inhibitors and having prophylactic treatment during 2023, split by age. The committee noted that separate usage data was available for people under 12 years and 12 years and over. This could be applied to model factor VIII replacement therapy distributions in PUPs and PTPs. The company highlighted that this approach assumed that all PTPs were 12 years and over and that relative usage data for people under 12 years was generalisable for all PUPs. This may not be the case in clinical practice. The committee thought that this dataset was the most relevant to the decision problem and preferred to use it for analyses in which relative market share was included. But it noted that not all PTPs were 12 years and over, which increased uncertainty in the results.

Treatment effectiveness in the model

3.17 The company's model estimated the cost effectiveness of efanesoctocog alfa compared with comparators using the following evidence sources:

- The quality-adjusted life years were determined by the number of treated and untreated bleeds. These were calculated using the proportion of people with a bleed each cycle and, to determine the bleeding rate in people with bleeds, the ABRs for treated bleeds and any bleeds.
- The costs were estimated using the proportion of bleeds treated (based on the ABR for treated bleeds).

  In the company's base case, after consultation, the key efficacy inputs for efanesoctocog alfa came from arm A of XTEND-1, arm D of HAVEN-3 for emicizumab and the pooled arms of A-LONG for efmoroctocog alfa (see section 3.12). In its base case, the company calculated the ABRs for any bleed and any treated bleed for efanesoctocog alfa, efmoroctocog alfa, turoctocog alfa pegol and emicizumab. It did this by applying the IRR from the MAIC adjusting XTEND-1 and A-LONG to the HAVEN-3 population to the ABRs from HAVEN-3. The ABR for any bleed was not collected in A-LONG, so the company assumed that the IRR for treated bleeds and any bleed was equal for EHLs. The comparisons to SHL factor VIII replacement therapies were informed by the intrapatient comparison in XTEND-1, which compared prophylactic efanesoctocog alfa with prior SHL factor VIII replacement therapy (see section 3.13). The committee acknowledged the uncertainty surrounding the relative-effectiveness results (see section 3.14). But it concluded that the company's approach to applying treatment effect in the model was the most appropriate option given the available evidence.

Health-related quality of life

Company's utility values

3.18 The company assumed that people without bleeds and factor VIII levels above 50% would have the same quality of life as the age-adjusted general public. The

company applied 2 disutilities for people who had a bleed:

- a short-term disutility applied for 7 days to reflect the pain and discomfort of bleeding, and the burden of further factor VIII injections
- a long-term disutility applied for the full 6-month cycle, to capture anxiety related to the risk of a further bleed and limits to daily activities.

The company calculated the short- and long-term disutilities using Tobit models, which were fitted to quality-of-life data from XTEND-1 (in efanesoctocog alfa) and A-LONG and ASPIRE (in efmoroctocog alfa). At the first meeting, the committee also had concerns about the company's approach to modelling utilities because:

- It assumed that the results of the Tobit models, which used EQ-5D data from people having factor VIII replacement therapies, would be relevant to emicizumab. The committee thought that this was unlikely to be appropriate because of the differences in treatment frequency and method of administration (intravenous compared with subcutaneous) between factor VIII replacement therapies and emicizumab.
- It assumed the type, severity and location of bleeds were identical for the different treatments under evaluation.
- It did not capture the impact of chronic pain from subclinical bleeds on quality of life.

At consultation, the company provided scenarios varying the disutility for people having 2 or more injections per week (disutility rates were taken from the CHESS II study and ranged between -0.027 and -0.107), but not by administration route. This was because a study by Muhlbacher et al. (2020) suggested that quality of life was not affected by administration route. The company also said that, because the ITC results for joint and non-joint bleeds were similar, location was expected to have minimal impact on bleeding rates. Also, the impact of chronic pain was captured through correlation with factor VIII activity levels, which was likely conservative. This was supported by XTEND-1 PROMIS Pain Intensity score results, which suggested reduced pain with efanesoctocog alfa prophylaxis compared with prestudy factor VIII replacement therapy. At consultation, the company provided 4 extra Tobit

models varying the coefficients included. It also provided scenario analyses using linear models to derive utilities. Its preferred Tobit model was unchanged from the first meeting and chosen for the best fit to the trial data and because it included the company's preferred disutility for low factor VIII activity levels (see section 3.19). The EAG was concerned that the company's chosen model included days since starting treatment as a coefficient, but this outcome was not included in the economic model. The EAG's base case after consultation used a Tobit model that excluded this outcome and had the best fit to the data of these options. The committee agreed that this was appropriate. But it remained concerned that the company's approach to modelling utilities did not include data for emicizumab from HAVEN-3. It thought that it was unlikely that quality-of-life data for factor VIII replacement therapies was generalisable to people having emicizumab. So, the modelled utility values likely underestimated the quality of life of people having emicizumab. The committee thought that this may have biased the model against emicizumab. It concluded that the Tobit model outputs were highly uncertain.

Disutility by factor VIII activity level

3.19 The company also applied a disutility for people whose factor VIII activity levels were under 20%. This was based on clinical expert opinion to the company that the higher risk of bleeds in people with lower factor VIII activity levels can cause anxiety and limit daily activities. The EAG highlighted that, although low factor VIII activity levels were associated with reduced quality of life in XTEND-1, levels were monitored more frequently than they would be in clinical practice. If people were unaware of low factor VIII activity levels, they would be unlikely to limit activities or have anxiety over the risk of bleeds. So, the company's approach may have overestimated the disutility in people with low factor VIII activity levels. At the first committee meeting, the patient experts said that they were likely to be more cautious and adjust their daily activities if they knew their factor VIII activity levels would be low. They would be aware that their factor VIII activity levels would be low shortly before their next dose. This would be the case even if they had not measured their factor VIII activity levels. One clinical expert estimated that people were unlikely to have spontaneous bleeds with factor VIII activity levels of over 10% or bleeds after minor trauma with levels of over 15%.

The company acknowledged this but said that the disutility should apply to the threshold at which people would change behaviour. This may be above that at which spontaneous bleeds occur. So, it maintained a disutility for factor VIII activity levels of under 20% in its base case but provided scenarios at lower thresholds. It claimed that this was supported by data from the PROPEL study. This study reported higher rates of total, spontaneous, joint and traumatic bleeds for people with factor VIII activity levels lower than 20% compared with levels over this threshold. The EAG agreed there was the likely correlation between quality of life and low factor VIII activity levels, but the threshold at which this applied was uncertain. It preferred the Tobit model that included a disutility for factor VIII activity levels of under 5%.

At the first meeting, the committee noted that the company had modelled everyone having emicizumab as having factor VIII levels of between 5% to 20%. This was based on a study by Shima et al. (2016) in non-human primates. So, 100% of people having emicizumab accrued a disutility for having low factor VIII activity levels. After consultation, the company updated this assumption so that only 30% of people having emicizumab accrued this disutility. This was based on factor VIII-like activity levels reported in a paper by Kizilocak et al. (2021). It also provided scenarios in which there was no disutility associated with factor VIII activity levels for people having emicizumab. The committee considered whether it was appropriate to apply a disutility based on factor VIII activity at all for people having emicizumab. It noted that emicizumab does not work by replacing factor VIII, so factor VIII activity levels cannot be used to measure bleeding protection. One clinical expert at the second meeting supported this, stating that there is significant variation in protection levels against bleeds that cannot be linked to factor VIII-like activity. The committee agreed that it was plausible that having low factor VIII activity levels reduced quality of life in people having factor VIII replacement therapies. But it was unclear whether low factor VIII activity levels would affect quality of life in people having emicizumab. It considered the scenarios in which no factor VIII activity utility decrement was applied for people have emicizumab. It noted that this did not change the direction of the decision making. The committee was also concerned that people with a factor VIII activity level of 20% were classed as having mild haemophilia A, so would have a relatively low risk of bleeding. It recalled that there were substantial limitations to the company's approach to capturing utilities using Tobit models. It thought that the EAG's preferred utility model, which included a

disutility from factor VIII activity levels of under 5%, better reflected the inputs of the economic model (see section 3.18). It preferred to apply this.

Costs and resource use

Dose of on-demand efanesoctocog alfa for bleeds

3.20 The company's model assumed that a proportion of people with bleeds each cycle would need further treatment with on-demand factor VIII therapies (see section 3.15). People having prophylactic treatment with a factor VIII replacement therapy had on-demand treatment with the same therapy that they had prophylactically. People having prophylactic emicizumab had on-demand octocog alfa. At the first committee meeting, the EAG was concerned that the company had modelled a 50 IU/kg on-demand dose for efmoroctocog alfa and octocog alfa, but only 25 IU/kg for efanesoctocog alfa. The company based this on clinical expert opinion that the sustained pharmacokinetic profile of efanesoctocog alfa would mean a lower dose would be effective at controlling bleeds. The EAG noted that XTEND-1 used an on-demand dose of 50 IU/kg to treat bleeds that occurred on efanesoctocog alfa prophylaxis. If the bleeding episode did not resolve, additional doses of 3 or 50 IU/kg could be administered every 2 or 3 days, as needed. It noted that, in XTEND-1, 77% of people with a bleed on efanesoctocog alfa prophylaxis in arm A had around 50 IU/kg efanesoctocog alfa to stop bleeding. So, there was no clinical-effectiveness data using the company's preferred dose of 25 IU/kg. For this reason, the EAG used a dose of 50 IU/kg for bleeds for all modelled treatments in its base case. The patient experts confirmed that, in their experience of treating bleeds with on-demand efanesoctocog alfa in XTEND-1, 1 dose of 50 IU/kg was usually sufficient in controlling bleeds to an extent to which people could work and carry out daily activities. They explained that many people prefer to avoid further retreatment after the initial on-demand dose unless their symptoms worsen. So, it was unlikely that an extra 30 IU/kg would be used in clinical practice. At consultation, the company updated its base case to use 50 IU/kg of efanesoctocog alfa for bleeds. The committee concluded that a dose of 50 IU/kg of efanesoctocog alfa for treating bleeds occurring on prophylaxis should be used to align with data from XTEND-1.

Wastage costs

3.21 The company included costs for treatment acquisition and bleed management in its model. It did not model any treatment administration costs because treatments are self-administered. In its original submission, it assumed wastage costs only for octocog alfa, the on-demand treatment for people having emicizumab (see section 3.20). At the first meeting, the patient experts highlighted that, for people on emicizumab, additional vials of factor VIII replacement therapy are needed at home for on-demand treatments. These can be wasted if no bleed occurs during the lifetime of the product (around 2 years in the fridge). At the first meeting, the committee noted that there would be no excess vials thrown away. But it was concerned that the NHS cost of people using a higher dose than needed was not reflected in the company's model. At consultation, the company updated its base case to model wastage costs for all prophylactic treatments for adults, but not for children and young people. This was based on clinical expert opinion that vial usage does not consistently reflect weight variations because of growth. So, modelling wastage in children and young people is complex. The company also updated its approach to modelling wastage costs for octocog alfa at consultation. The EAG agreed with this approach. The committee concluded that the company's updated approach to modelling wastage costs in the model was appropriate for decision making.

Cost of managing bleeds

3.22 The company assumed that each bleed incurred a cost for management, including emergency, specialist and nurse visits. The number of emergency and specialist visits was based on Shrestha et al. (2017). Because this paper reported the need for multiple specialist visits per bleed, the company assumed that no additional nurse visits would be needed in its original submission. The company's clinical experts also confirmed that people would be keen to avoid emergency visits if possible, and that bleeds are often managed by a combination of in-person and telephone consultations with specialists. The EAG noted that most bleeds in XTEND-1 were joint and muscle bleeds that resolved with 1 injection, so were likely mild to moderate. It thought that mild to moderate bleeds would likely be managed over the phone and often by specialist nurses instead of doctors. At consultation, the company updated its approach to retain the same number of

contacts per bleed. But it weighted costs across consultant and non-consultant led face-to-face and phone outpatient contacts. The committee thought that the company's updated approach to modelling bleed management costs was appropriate.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates in PUPs

3.23 After consultation, the company provided an updated base case including:

- a MAIC for efanesoctocog alfa, efmoroctocog alfa and emicizumab, which adjusted both the A-LONG and XTEND-1 trial populations to aggregate data from HAVEN-3 using prophylactic arms of HAVEN-3 (arm D) and XTEND-1 (arm A), and pooled arms of A-LONG (see section 3.12)
- an on-demand dose of 50 IU/kg of efanesoctocog alfa for treating bleeds while having prophylaxis (see section 3.20)
- updated drug wastage and bleed management costs (see section 3.21 and section 3.22).

For PUPs, the company's base case included a fully incremental analysis of efanesoctocog alfa compared with efmoroctocog alfa and emicizumab. The company also presented a scenario analysis including simoctocog alfa as a comparator. The committee noted that not all SHLs available in the NHS were included by the company for PUPs (see section 3.5). The EAG also presented an updated base case. This was aligned with the company's updated base case. But the EAG included SHLs as comparators in its base case and applied a different Tobit model for calculating disutilities because of bleeds (see section 3.18). Because of confidential commercial arrangements for efanesoctocog alfa, the comparators and other treatments in the model, the exact cost-effectiveness estimates are confidential and cannot be reported here. In PUPs, efanesoctocog alfa was dominant (less costly and more clinically effective) compared with the other available EHLs and emicizumab in both the company's and EAG's base cases. It was not cost effective

compared with a basket of SHLs in the EAG base case.

Company and EAG cost-effectiveness estimates in PTPs

3.24 For PTPs, the company's base case included a fully incremental analysis of:

- efanesoctocog alfa compared with efmoroctocog alfa, turoctocog alfa pegol and emicizumab
- efanesoctocog alfa compared with a weighted basket of EHLs (assuming 50% of people had efmoroctocog alfa and 50% of people had turoctocog alfa pegol).

  The company also presented a scenario analysis including a weighted basket of SHLs as a comparator with the weights taken from UKHCDO annual report data (see section 3.16). As in PUPs, the EAG's base case aligned with the company's updated base case. But it included SHLs as comparators in its base case and applied a different Tobit model for calculating disutilities due to bleeds (see section 3.5 and section 3.18). Because of confidential commercial arrangements for efanesoctocog alfa, the comparators and other treatments in the model, the exact cost-effectiveness estimates are confidential and cannot be reported here. In PTPs, efanesoctocog alfa was not the most cost-effective treatment available for haemophilia A when applying the company and EAG's preferred assumptions. The committee noted that, in pairwise analyses, efanesoctocog alfa was dominant compared with emicizumab in both the company and EAG base cases for PUPs and PTPs.

The committee's preferences

3.25 For the cost-effectiveness results in PUPs, the committee preferred the model to:

- include efmoroctocog alfa, emicizumab and a basket of SHL factor VIII replacement therapies (octocog alfa, simoctocog alfa, turoctocog alfa and moroctocog alfa) as the relevant comparators (see section 3.5)

- weight the basket of SHL factor VIII replacement therapies by market share according to UKHCDO data in people with severe haemophilia A and no inhibitors, and who had prophylactic treatment during 2023, split by age (see section 3.16).

For the cost-effectiveness results in PTPs, the committee preferred the model to:

- include a basket of EHL factor VIII replacement therapies (efmoroctocog alfa and turoctocog alfa pegol), emicizumab and a basket of SHL factor VIII replacement therapies (octocog alfa, simoctocog alfa, turoctocog alfa and moroctocog alfa; see section 3.6)
- weight the baskets of SHL and EHL factor VIII replacement therapies by market share according to UKHCDO data in people with severe haemophilia A and no inhibitors, and who had prophylactic treatment during 2023, split by age (see section 3.16).

The committee agreed that several of the modelled inputs were highly uncertain but, given the options available, it preferred analyses including:

- the company's and EAG's base-case MAIC from the second meeting aligning the XTEND-1 and A-LONG trial populations to that in HAVEN-3 and adjusting for baseline ABR to inform the treatment effect for efanesoctocog alfa compared with emicizumab and efmoroctocog alfa
- assuming a class effect for EHLs and SHLs, and using the treatment effect for SHLs from the intrapatient comparison
- the EAG's preferred Tobit model for health-state utilities, including a disutility for factor VIII activity levels of under 5%.

Using its preferred assumptions, and with the confidential commercial discounts applied, efanesoctocog alfa was cost effective compared with:

- a basket of EHL factor VIII replacement therapies in PUPs but not in PTPs
- a basket of SHL factor VIII replacement therapies in PTPs but not in PUPs.

The committee noted that efanesoctocog alfa was dominant compared with emicizumab in both PUPs and PTPs. But the committee recalled the substantial uncertainty in the model inputs. This included the unanchored MAIC and the utility values used, and likely biased the results against emicizumab (see section 3.14 and section 3.18). So, the committee thought that there were significant uncertainties about:

- whether efanesoctocog alfa was more clinically effective than emicizumab
- the relative effectiveness of efanesoctocog alfa compared with EHL and SHL factor VIII replacement therapies.

But it noted that efanesoctocog alfa was likely cheaper than emicizumab. The committee thought that the incremental cost-effectiveness results were informative but associated with substantial uncertainties.

Analyses using a basket of current haemophilia A treatments

3.26 The committee noted that there was substantial uncertainty about the clinical effectiveness of efanesoctocog alfa compared with current treatments (see section 3.14). It also noted that there was heterogeneity in the treatments used for severe haemophilia A, largely due to the different preferences of people with haemophilia A (see section 3.4). So, as well as the incremental analyses, the committee thought that it was appropriate to consider analyses comparing efanesoctocog alfa with a combined basket of haemophilia A treatments, including SHL and EHL factor VIII replacement therapies and emicizumab. The committee considered cost-effectiveness results in which efanesoctocog alfa was compared with a weighted basket of available treatments using the committee's preferred assumptions (see section 3.25). The weighting was based on market share according to UKHCDO data in people with severe haemophilia A and no inhibitors, split by age, who had prophylactic treatment during 2023 (see section 3.16). The committee noted that the proportion of people having SHLs in NHS practice is small and decreasing, and that most people with severe haemophilia A have emicizumab (see section 3.4). The committee noted that, in PUPs, efanesoctocog alfa was dominant compared with a weighted basket of available treatments. In PTPs, the incremental cost-effectiveness ratio for

efanesoctocog alfa compared with a weighted basket of available treatments was below the threshold usually considered a cost-effective use of NHS resources. The committee also considered the total annual treatment costs per person for efanesoctocog alfa compared with a weighted basket of available treatments. It noted that the annual treatment costs for efanesoctocog alfa were less than the weighted basket for PUPs but greater than the weighted basket for PTPs. It also noted the annual treatment costs for efanesoctocog alfa compared with emicizumab. The committee also considered the total impact on NHS budgets associated with introducing efanesoctocog alfa. It took this into account when considering the decision risk of recommending efanesoctocog alfa was relatively low. The committee considered all the available evidence, including the fully incremental analyses and the analyses using a basket of available treatments (see section 3.25 and section 3.26). It concluded that efanesoctocog alfa was likely to represent a cost-effective use of NHS resources, so could be recommended.

Other factors

Equality

3.27 The committee noted that people who carry the haemophilia gene may have mild or, rarely, moderate to severe symptoms of bleeding. It noted that all carriers of haemophilia A have XX chromosomes, so carrier status is affected by biological sex. But it recalled that it had not been presented with any evidence for the mild or moderate haemophilia A populations, and that mild haemophilia A was outside the marketing authorisation for efanesoctocog alfa. It also noted that a recommendation in severe haemophilia A would not be restricted by biological sex. It recalled that there were differences in the treatment pathway and potential treatment effect. These differences meant clinical- and cost-effectiveness outcomes would likely be different between people with severe and mild to moderate haemophilia A (see section 3.2). So, it could not make a recommendation for this population. Stakeholders also highlighted that some of the treatments for haemophilia A, including efanesoctocog alfa, are derived from human blood or human or animal cells. This may not be considered acceptable by people with some religious beliefs. The committee was aware that there are

several treatment options from different sources that people may choose. These include emicizumab, which is not derived from human blood products. The committee did not identify this as an equalities issue that would affect its recommendations. At consultation, clinical experts highlighted that children would be disproportionately affected by a negative recommendation in this population. This is because they are typically the most active subgroup of the haemophilia A population. So, they are the most at risk of trauma-induced bleeding. The committee acknowledged the impact of the condition and treatment on children. It thought that its recommendation would include all people with severe haemophilia A 2 years and over. The only restriction based on age, to age 2 years and over, was required by the marketing authorisation. It concluded that all equalities issues for efanesoctocog alfa had been considered in its decision making.

Uncaptured benefits

3.28 The committee noted that some potential benefits of efanesoctocog alfa may not have been included in company's model. The company, and the patient and clinical experts described the uncaptured benefits of weekly dosing of efanesoctocog alfa, compared with more frequent dosing of factor VIII replacement therapies, including:

- a reduced treatment burden for people with the condition and their carers (especially considering that severe haemophilia A may affect several siblings in the same family)
- improved vein health, especially in older people who have been using factor VIII replacement therapies for a long time; the committee thought it unlikely that the need for a venous access device for children would decrease because weekly injections would still be needed
- improved treatment adherence
- freedom to travel and participate in sports more easily, which can reduce obesity levels and related comorbidities in later life.

The company, and the patient and clinical experts also explained the

uncaptured benefits of maintaining higher factor VIII levels for longer, including:

- a reduced need for emergency treatment, especially for children who have frequent traumatic bleeds from normal daily activity
- reduced anxiety about the risk of bleeds for people with haemophilia A and their carers
- improved educational attainment from fewer school and work absences for treatment
- improved relationship with healthcare providers from a young age
- less fear and resentment of the condition
- the ability to live with a 'haemophilia free mindset' and do activities with a high risk of bleeds.

The committee concluded that there might be additional benefits with efanesoctocog alfa that were not captured in the cost-effectiveness analysis. It considered these as part of its decision making.

Conclusion

Efanesoctocog alfa is recommended

3.29 The committee understood the impact of the condition and the potential benefits of efanesoctocog alfa, and noted evidence that it is a clinically effective treatment option. It recalled that there were considerable uncertainties in the relative-effectiveness evidence and economic model. This included uncertainties in the ITC and how utility values were incorporated into the model. It thought that these uncertainties likely biased the modelling towards efanesoctocog alfa, especially when compared with emicizumab. The committee considered the fully incremental analyses, applying their preferred assumptions (see section 3.25) and analyses comparing efanesoctocog alfa with a basket of available treatments (see section 3.26). Considering all the available evidence, it concluded that

efanesoctocog alfa is a cost-effective use of NHS resources. So, efanesoctocog alfa is recommended in people 2 years and over with severe haemophilia A.

4 Implementation

4.1 Section 7 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 technology appraisal guidance. When a NICE technology appraisal 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 efanesoctocog alfa and the healthcare professional responsible for their care thinks that efanesoctocog alfa 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 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.

Emma Douch
Technical lead

Lizzie Walker
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