NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Efanesoctocog alfa for treating and preventing bleeding episodes in haemophilia A

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

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

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

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

Issue date: May 2024

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

After consultation:

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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using efanesoctocog alfa in the NHS in England.

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

The key dates for this evaluation are:

  - Closing date for comments: 10 June 2024
  - Second evaluation committee meeting: TBC

- Details of membership of the evaluation committee are given in section 4

1 Recommendations

1.1 Efanesoctocog alfa is not recommended, within its anticipated marketing authorisation, for treating and preventing bleeding episodes in people with haemophilia A (congenital factor VIII deficiency).

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, the company asked for efanesoctocog alfa to be considered only for people with severe haemophilia A. This does not include everyone who it is anticipated to be licensed for.

Current treatment for severe haemophilia A includes factor VIII replacement therapies (such as efmoroctocog alfa) or emicizumab to prevent bleeding, and on-demand factor VIII replacement therapies to treat bleeding.

The results from 1 clinical trial show fewer bleeding episodes for people having ongoing efanesoctocog alfa compared with on-demand efanesoctocog alfa. There is limited clinical-effectiveness evidence from direct comparisons of efanesoctocog alfa with any other treatment for severe haemophilia A. An indirect comparison suggests that efanesoctocog alfa may reduce the number of bleeding episodes compared with efmoroctocog alfa. The results of an indirect comparison of efanesoctocog alfa with emicizumab are unreliable, so whether one works better than the other is unknown.

It is not possible to reliably estimate the cost effectiveness of efanesoctocog alfa because:

- of the uncertainties in the clinical-effectiveness evidence and economic modelling
- the company did not provide evidence comparing it with all relevant factor VIII replacement therapies.

So, efanesoctocog alfa is not recommended.

2 Information about efanesoctocog alfa

Anticipated marketing authorisation indication

2.1 Efanesoctocog alfa (Altuvoct, Swedish Orphan Biovitrum) does not have a marketing authorisation in Great Britain yet. The Committee for Medicinal Products for Human Use (CHMP) has adopted a positive opinion recommending the granting of a marketing authorisation for the medicinal product efanesoctocog alfa, intended for the treatment and prophylaxis of bleeding in people with haemophilia A (congenital factor VIII deficiency).

Dosage in the marketing authorisation

2.2 The dosage schedule will be 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). It is available as 250 IU, 500 IU, 750 IU, 1000 IU, 2000 IU, 3000 IU, 4000 IU vials.

2.4 The company has a commercial arrangement, which would have applied if the efanesoctocog alfa had been recommended.

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 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 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 NICE scope and anticipated licence for efanesoctocog alfa includes everyone with haemophilia A. But the decision problem in 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 mild or moderate haemophilia A from its decision problem because there was no evidence for efanesoctocog alfa in these groups. Also, it did not expect efanesoctocog alfa to be routinely used in these groups. 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 mild to moderate haemophilia A. Also, it considered 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 mild to moderate haemophilia A. So, it was unable to make recommendations for using efanesoctocog alfa in mild to 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 licensed for prophylaxis in the NHS (all every 2 to 3 days) are:
  - octocog alfa

  - simoctogog alfa
  - morcotogog alfa

  The extended half-life (EHL) factor VIII replacement therapies licensed 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
  - rurioctocog alfa pegol, used every 3 to 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 severe 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 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 the 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, about 5% to 7% of people with 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. 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.
- It is not a factor VIII replacement therapy, so factor VIII activity levels are not monitored via a blood test. This means there is no clinical marker of protection from bleeds.
- 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 were treated subcutaneously 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 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

Comparators in the scope and company submission

3.5 The NICE scope considered the relevant comparators for efanesoctocog alfa to be established clinical management, including:

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

The company submission included the following comparators:

- For PUPs:
  - an EHL factor VIII replacement therapy, efmoroctocog alfa (prophylaxis and on-demand)
  - emicizumab (prophylaxis), with an SHL factor VIII replacement therapy, octocog alfa (on-demand)
- For PTPs:
  - emicizumab (prophylaxis), with an SHL factor VIII replacement therapy, octocog alfa (on-demand).

The committee noted that that the SHL factor VIII replacement therapies used in the NHS are octocog alfa, simoctocog alfa and morcotocog alfa. Although included in the scope, SHLs were excluded by the company as relevant comparators for efanesoctocog alfa for both PUPs and PTPs. This was because market share data from people with severe haemophilia A suggested that emicizumab use is increasing and SHL factor VIII replacement therapy use is declining. One clinical expert highlighted UK National Haemophilia Database data showing that over 60% of people with severe haemophilia A in the NHS now have emicizumab and under 20% have SHL factor VIII replacement therapies. But another clinical expert stated that SHL factor VIIII replacement therapies are still used by many people with severe haemophilia A. The EAG highlighted that a substantial proportion of people still had SHL factor VIII replacement therapies. So, the committee considered that SHL factor VIII replacement therapy was a relevant comparator for efanesoctocog alfa.

Relevant comparators in PUPs

3.6 In light of the evidence provided, the committee first considered the relevant comparators for PUPs. The clinical experts explained that subcutaneous administration is the only option for children until their veins are sufficiently robust to have intravenous injections. In some treatment

centres, people start having emicizumab from diagnosis and then are offered SHL factor VIII replacement therapies or efmoroctocog alfa. The clinical experts explained that efmoroctocog alfa is the only EHL licensed for people under 12 years and that other EHLs are not used off-licence in young people. In some treatment centres, people start by having SHL factor VIII replacement therapies or efmoroctocog alfa, especially for children who are diagnosed with haemophilia A after the first few months of life. So, the committee concluded that emicizumab, SHL factor VIII replacement therapies (octocog alfa, simoctocog alfa or morcotocog alfa) and efmoroctocog alfa were all relevant comparators in PUPs.

Relevant comparators in PTPs

3.7 The committee next considered the relevant comparators for efanesoctocog alfa in PTPs. It noted that the company had not included EHL factor VIII replacement therapy as a comparator (see section 3.5). This was because the company considered that efanesoctocog alfa would be used after EHL factor VIII replacement therapies in clinical practice. The committee noted data from the National Haemophilia Database about factor VIII therapy use in the NHS for severe haemophilia in people 12 years and over. This suggested that both SHL (octocog alfa, simoctocog alfa or morcotocog alfa) and EHL (efmoroctocog alfa, turoctocog alfa pegol or rurioctocog alfa pegol) factor VIII replacement therapies are used. The committee acknowledged that some PTPs were likely to be under 12 years, so would not be able to have turoctocog alfa pegol or rurioctocog alfa pegol. It 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. So, it agreed that the company's choice to exclude factor VIII replacement therapy as a comparator in PTPs was not justified. It concluded that the relevant comparators in PTPs were emicizumab, and SHL (octocog alfa, simoctocog alfa or morcotocog alfa)

and EHL (efmoroctocog alfa, turoctocog alfa pegol or rurioctocog alfa pegol) factor VIII replacement therapies.

Clinical evidence

Data sources

3.8 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 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 74 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 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 were hard to measure because they relied on patient reporting. The committee noted several limitations with the XTEND-1 trial design:

- There was no control arm comparing efanesoctocog alfa with the 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 had emicizumab.
- There is a high risk of bias when using intrapatient comparisons instead of comparing with a control arm, including placebo effect and effect of being in a clinical trial. The committee noted that people in XTEND-1 had high bleeding rates. It also noted that it was likely that some people would have improvement in bleeding rates over time regardless of treatment (regression to the mean), which could be wrongly considered as a treatment effect.

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

Trial results

3.9 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 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 companies 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 or not 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 3.8). 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

3.10 The NICE scope and anticipated licence for efanesoctocog alfa included all people with haemophilia A. The EAG highlighted that the population in XTEND-1 was narrower than the scope and anticipated licence for efanesoctocog alfa because it excluded:

- people with mild and 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 without 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 or not 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 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.

Indirect treatment comparison (ITC)

Methodology of the company's ITC with emicizumab

3.11 There were no trials directly comparing efanesoctocog alfa with emicizumab, so the company did an 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 stated that an unanchored MAIC was needed because there was no common comparator across XTEND-1 and HAVEN-3. To do the MAIC, first the company removed people from XTEND-1 with baseline characteristics outside of the range reported for HAVEN-3. The remaining XTEND-1 population was then weighted to balance covariates with HAVEN-3. The covariates adjusted for varied by analysis but included age, body weight, presence of target

joints and most abundant ethnic groups. The company did several analyses, varying arms from HAVEN-3 and XTEND-1, and pooling data from all arms of each trial. Its preferred arms for use in the MAIC were arm B of HAVEN-3 and arm B of XTEND-1, both of which included people who had had an on-demand regimen. This was because arm B of HAVEN-3 used 2-weekly emicizumab administration, which the company's clinical experts expected to be most used in NHS practice. The EAG was concerned that the covariates matched in the company's MAIC differed depending on which trial arms were used. The company stated that this was because of small numbers of people in its preferred arms. The outcomes of the MAIC also differed by analysis. They included ABRs for any bleed, any treated bleed, spontaneous treated bleeds and joint treated bleeds and, for pooled trial data, Haemophilia Joint Health Score. The EAG preferred to use arm D of HAVEN-3 and arm A of XTEND-1, both of which included people who had had prophylaxis. This was because it substantially increased the effective sample size for both the HAVEN-3 and XTEND-1 arms. The committee noted the inherent uncertainty in unanchored MAICs. This is because they assume that all prognostic variables and effect modifiers have been accounted for in the adjustment. The committee noted that people in HAVEN-3 had a higher bleeding rate at study entry than people in XTEND-1. This suggested that the population in HAVEN-3 had more severe disease or the measurement of bleeds differed across trials. The committee noted that baseline bleeding rate was likely a prognostic factor that had not been adjusted for in the company's unanchored MAIC compared with emicizumab. It thought this may have biased the results. The MAIC also adjusted the population to the comparator trial (in this case, HAVEN-3), so assumed that this trial represents people with the condition in the NHS. The committee also recalled the inconsistency in the company's matched covariates and outcomes depending on the arms used in the analysis and the small sample sizes after matching. Because of this, the committee concluded that the company's MAIC comparing emicizumab with

efanesoctocog alfa had significant limitations. It thought that it was unlikely to provide reliable estimates of relative clinical effectiveness between treatments.

Methodology of the company's ITC with efmoroctocog alfa

3.12 There were no trials directly comparing efanesoctocog alfa with efmoroctocog alfa. So, the company did an ITC using a propensity score matching (PSM) approach to establish the relative efficacy. 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 stated that there was no common comparator in XTEND-1 and A-LONG. Because the company had individual patient data available from A-LONG, it used a PSM approach for the ITC. In this, it weighted individual data from each trial (pooling all arms) to balance baseline characteristics. The outcomes of the PSM included ABRs for any treated bleed, spontaneous treated bleeds and treated bleeds in joints. The proportions of people without bleeds, factor VIII consumption and quality of life were also compared across trials. The baseline characteristics adjusted included age, body weight, proportion with prior prophylaxis, presence of target joints and number of prior bleeds. The EAG was concerned about the lack of justification of baseline characteristics chosen for adjustment, but used the same assumptions as the company in its preferred analyses. The committee noted an unanchored comparison assumes that all prognostic variables and effect modifiers have been adjusted for. It noted that, if the adjustments are not appropriate, the

results of the PSM are uncertain. 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. It concluded that there was uncertainty surrounding the adjusted variables that made the analyses uncertain. But it considered that, in the context of the evidence available, the PSM was informative for decision making.

Results of the ITC

3.13 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 noted that only the comparison of ABR for any bleed was statistically significant. Using the EAG's preferred arms showed similar results. The IRR ABR for any bleed was 0.32 (95% CI 0.19 to 0.56) and for any treated bleed was 0.50 (95% CI 0.29 to 0.86). 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). The committee recalled that the methodology in the unanchored MAIC with emicizumab and, to a lesser extent, the PSM with efmoroctocog alfa were uncertain (see section 3.11 and section 3.12). It questioned the face validity of the company's results when incorporating the company's preferred IRRs from the MAIC and PSM into the model. This was because the ABR for any bleed with emicizumab was higher than that with efmoroctocog alfa. This contrasted with the results for any treated bleed, in which the ABR was lower for emicizumab than for efmoroctocog alfa. The committee considered that this raised concerns about the ITCs and the evidence they were based on because:

- The clinical experts considered that the difference in effectiveness between emicizumab and factor VIII replacement therapies such as efmoroctocog alfa was uncertain (see section 3.4)

- In clinical practice, most people have emicizumab (see section 3.4), and people are most likely to choose the treatment that they consider to be most effective.

The committee noted that results from an intrapatient comparison from HAVEN-3 in 48 patients. These suggested that emicizumab statistically significantly reduced the ABR for any treated bleed in people who switched from factor VIII replacement therapies (rate ratio 0.32, 95% CI, 0.20 to 0.51; p<0.001). But HAVEN-3 had not reported a comparison for emicizumab compared with factor VIII replacement therapies for any bleed. The committee noted that the ITCs with emicizumab and efmoroctocog alfa also adjusted to different populations, and that the populations in each trial appeared noticeably different (see section 3.11 and section 3.12). The committee considered that this might explain that lack of face validity of the results. It concluded there were significant uncertainties about methodology and results of the company's ITCs.

Conclusions of relative effectiveness data

3.14 The committee concluded that the results of the company's ITCs were not appropriate for decision making. This was because of concerns with the methodology of the ITC (see section 3.11, section 3.12 and section 3.13), and the lack of face validity of the results. It agreed that multiple alternative approaches should be explored to estimate the effectiveness of efanesoctocog alfa compared with the relevant comparators, either directly or through an indirect comparison. These should include but not necessarily be limited to:

- A MAIC adjusting both the A-LONG and XTEND-1 populations to the aggregate data from HAVEN-3: the committee acknowledged that a PSM approach is normally preferred when individual patient data is available (see section 3.11 and section 3.12). But the committee noted the differences in the trial populations. It thought that adjusting both A-LONG and XTEND-1 to the HAVEN-3 population should be explored

to compare the relative effects of each comparator with efanesoctocog alfa after adjustment to the same population (that of HAVEN-3).

- Exploring methods to anchor an ITC by:
  - Using the on-demand arms in each trial: the EAG highlighted that the treatments considered as on-demand differed by trial (efanesoctocog alfa in XTEND-1, efmoroctocog alfa in A-LONG and SHL factor VIII replacement therapies in HAVEN-3). There was also no randomisation between the on-demand and prophylaxis arms in XTEND-1 and A-LONG, implying the need for an unanchored comparison. But the committee noted that both the Institute of Clinical and Economic Review and Canada's Drug and Health Technology Agency had done a network meta-analysis for emicizumab compared with factor VIII replacement therapies. The committee considered that 1 possible approach to include XTEND-1 in a network would be to do a PSM between arms A and B. This would provide a relative effect adjusted for confounders. After this, the on-demand arm could be used to anchor an indirect comparison, if all on-demand treatments are assumed to be equally effective.
  - The committee considered whether the intrapatient comparisons in XTEND-1 and HAVEN-3 could be used to anchor an ITC using prior SHL and EHL factor VIII therapy as the common comparator. The company highlighted that the standard care with factor VIII replacement therapies was different in the 3 trials. It also noted that people with haemophilia A switch treatments on a regular basis.
- The committee recalled that both SHL and EHL factor VIII replacement therapies were relevant comparators for efanesoctocog alfa (see section 3.6 and section 3.7). It considered that there was direct evidence available for efanesoctocog alfa compared with SHL and EHL factor VIII replacement therapies from the XTEND-1 intrapatient comparison. It considered that this direct evidence could be used to inform comparative clinical effectiveness in the economic model (see section 3.9), instead of doing an ITC.

The committee acknowledged the potential limitations of its suggested approaches, and that it was not known what approach would provide the most robust estimates of relative effectiveness for decision making. But it concluded that it would be valuable to explore several alternative approaches to generating comparative clinical-effectiveness data, including the data listed in section 14. The committee also concluded that the company should provide comparative clinical-effectiveness data for all relevant comparators (see section 3.6 and section 3.7).

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 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 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.

Treatment effectiveness in the model

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

- The quality-adjusted life years (QALYs) 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).

The key efficacy inputs for efanesoctocog alfa came from arm A of XTEND-1. For emicizumab, the company used the proportion of people with a bleed from arm D of HAVEN-3. It calculated the ABRs for any bleed and any treated bleed by applying the IRR from the MAIC (which used HAVEN-3 arm B and XTEND-1 arm B) to the ABRs from XTEND-1. The EAG considered it inappropriate to use different arms of HAVEN-3 to inform the efficacy inputs in the model, and so used the results of the MAIC comparing HAVEN-3 arm D and XTEND-1 arm A for the ABRs in its preferred base case. The committee agreed with the EAG's logic that the sources used for efficacy outcomes should be consistent. For efmoroctocog alfa, the proportion of people with a bleed and the ABR for treated bleeds were calculated by applying IRR from the PSM to XTEND-1 data. The ABR for any bleed was not collected in A-LONG, so the company assumed that the IRR for treated bleeds could be used to represent any bleed. The committee noted that, in the company's base case, the ABR for any bleed with emicizumab was 3.96. This was higher than that with efmoroctocog alfa, which was 3.83. The committee recalled that the company's ITC was not fit for decision making. This was because the MAIC and the PSM results lacked face validity and had substantial methodological limitations (see section 3.11, section 3.12 and section 3.13). It also noted that the impact on bleeding outcomes of potential adherence differences between subcutaneous and intravenous

treatments was uncertain and had not been explored by the company. The committee concluded that the treatment-effectiveness inputs used in the company's model were unacceptable for decision making because of the uncertainty in the ITC estimates. It also concluded that the company should provide comparative clinical-effectiveness data for all relevant comparators (see section 3.6 and section 3.7).

Health-related quality of life

Company's utility values

3.17 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. The EAG was concerned that the company's approach to capturing the implications of aging on utility in the economic model contradicted the evidence produced by the company's Tobit models. 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 efanesoctocog alfa in XTEND-1, would be relevant to efmoroctocog alfa and emicizumab. The committee considered that this was unlikely to be appropriate because of:
  - the differences in treatment frequency between efanesoctocog alfa, efmoroctocog alfa and emicizumab

  - the differences in 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.
- The company did not provide sufficient justification for its choice of preferred Tobit model from those tested.
- The company did not provide sufficient justification for its preferred parameter values from a set of Tobit model results, which it then applied as utility decrements in the economic model.

It concluded that the company's approach to capturing utilities was inappropriate. It thought that the company should further explore appropriate methods of modelling quality of life and further consider likely explanatory factors for quality-of-life differences across all relevant comparators. The committee recalled that the patient experts stated that method and frequency of treatment administration affected their quality of life (see section 3.4). So, it concluded that the company should do scenarios that included the impact of method and frequency of administration on utility values.

Disutility by factor VIII activity level

3.18 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 the XTEND-1 trial, these people 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. The patient experts stated that they were likely to be more cautious and adjust their daily activities if they knew their factor VIII activity levels would be low. The patient experts explained that 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 with minor trauma with levels of over 15%. The committee also noted 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. So, the committee agreed that applying a disutility for people with a factor VIII activity level of 20% was inappropriate. The committee also 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, everyone having emicizumab accrued a disutility for having low factor VIII activity levels. This was a much higher percentage than for people having efanesoctocog alfa and efmoroctocog alfa. The committee also 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. The committee recalled that the relative clinical effectiveness between treatments was unknown (see section 3.13). So, it was concerned that the company's approach to modelling a disutility for low factor VIII activity levels may have introduced a bias against emicizumab. The committee concluded that it was plausible that having low factor VIII activity levels reduced quality of life in people having factor VIII replacement therapies. But it considered that it was unclear whether having low factor VIII activity levels would affect quality of life in people having emicizumab. Also, the committee recalled that there were substantial limitations to the

company's approach to capturing utilities using Tobit models that affected the model (see section 3.17). It agreed that it would like to see:

- justification that factor VIII levels affect quality of life in people with haemophilia A and how they do this, including people who are having emicizumab
- modelling of quality of life that is consistent and coherent in how it reflects differences in quality of life between treatments (see section 3.17) and the effects of factor VIII levels
- a scenario in which disutility is applied to people with factor VIII activity levels of under 15%.

Costs and resource use

Dose of on-demand efanesoctocog alfa for bleeds

3.19 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 efanesoctocog alfa had on-demand treatment with efanesoctocog alfa and people on efmoroctocog alfa had treatment with efmoroctocog alfa. People having prophylactic emicizumab had on-demand octocog alfa. 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, followed by a further 30 IU/kg if 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. The committee noted that XTEND-1 showed that factor VIII levels were maintained to around 10% a week after injection. One clinical expert stated that a 50 IU/kg dose of efanesoctocog alfa would usually not be needed to increase the factor VIII activity levels to such an extent that the bleeding stops. The expert explained that the dose used would be based on bleed location and time since last injection. But the committee was concerned that the pharmacokinetics of on-demand and prophylactic therapy may be different. This is because stopping a bleed uses factor VIII faster than preventing a bleed, meaning that a higher dose of efanesoctocog alfa would be needed. The clinical experts confirmed that this was plausible. They highlighted that the half-life of factor VIII replacement therapies are reduced after surgery. The committee recalled that people would only have spontaneous bleeds if their factor VIII activity levels were under 15% (see section 3.18). So, the committee was concerned that a 25 IU/kg dose of efanesoctocog alfa may not be enough to stop the bleeding. The patient experts also highlighted that people having efanesoctocog alfa prophylactically would be likely to use the same dose for treating bleeds. This is because they would have this dose readily available and it would avoid wastage of unused vials at a lower dose. 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

3.20 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. It assumed wastage

costs only for octocog alfa, the on-demand treatment for people having emicizumab (see section 3.19), using the proportion of people in HAVEN-3 who remained bleed free on emicizumab. The company stated that wastage costs would not be relevant for efanesoctocog alfa, efmoroctocog alfa and emicizumab. This was because the number of doses used for prophylaxis was rounded up or down to a full vial by healthcare professionals. 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). The EAG highlighted that it considered the company's approach to modelling wastage of octocog alfa inappropriate. This was because it implied that the same people had bleeds each cycle, and the company had not justified the dose of octocog alfa assumed to be wasted. So, the EAG considered that the company should provide further justification, including consultation with clinical experts, for its approach. It also thought the company should consider revising its approach to modelling the expected wastage cost for octocog alfa. The committee recalled its preferred doses for treating bleeds with efanesoctocog alfa and efmoroctocog alfa aligned with those used for prophylaxis, which would minimise waste (see section 3.19). But the clinical experts highlighted that haemophilia A treatments are weight based. This means that people may 'round up' and use more drug than needed because of poor correlation between vial size and weight-based dose. So, although there would be no wastage (that is, no excess vials would be thrown away), the NHS cost of people using a higher dose than needed should be reflected in the model. The company's model did not account for this cost. The committee noted that the company had provided a scenario assuming wastage costs for emicizumab but not for efanesoctocog alfa or efmoroctocog alfa. So, the effect on the incremental cost-effectiveness ratio (ICER) was unknown. The committee concluded that the treatment costs for the amount of efanesoctocog alfa, efmoroctocog alfa, emicizumab and octocog alfa

expected to be used in clinical practice, including 'rounding up' of doses, had not been appropriately considered in the company's model. So, the committee thought that the company should amend its model to account for the expected use of each treatment in clinical practice.

Cost of managing bleeds

3.21 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. 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 considered that mild to moderate bleeds would likely be managed over the phone and often by specialist nurses instead of doctors. It also noted that the company had not used the most recent NHS reference costs and the costs for specialist nurse visits had increased substantially. So, the EAG was concerned that the company's assumption may not represent the costs of treating bleeds in the NHS. To account for this uncertainty, the EAG provided scenarios in which the current number of specialist visits were spread among specialists and nurse visits (to account for bleeds resolved by phone), and in which all resource use was because the management of bleeding episodes were omitted. The committee considered that, given the uncertainties highlighted by the EAG, the costs of managing bleeds was uncertain. It agreed that the company should provide further justification for its proposed bleed management costs and amend its approach to modelling these if necessary.

Cost-effectiveness estimates

Uncertainties in evidence and modelling assumptions

3.22 The committee noted that there were uncertainties in the evidence base and modelling assumptions, specifically:

- the comparators for efanesoctocog alfa (see section 3.6 and section 3.7)
- the effectiveness of efanesoctocog alfa compared with comparators from the ITC (see section 3.11, section 3.12 and section 3.13)
- the utility values used by the company, including any disutility for low factor VIII activity levels (see section 3.17 and section 3.18)
- wastage costs for efanesoctocog alfa and efmoroctocog alfa (see section 3.20)
- resource use and costs for managing bleeds (see section 3.21).

Company and EAG cost-effectiveness estimates

3.23 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. The ICERs for the comparisons against emicizumab (both in PUPs and PTPs) were within the range normally considered an acceptable use of NHS resources in both the company's and EAG's base cases. In the company's base-case analysis for the comparison against efmoroctocog alfa in PUPs, the ICER was within the range normally considered an acceptable use of NHS resources. In the EAG's base-case analysis for the comparison against efmoroctocog alfa in PUPs, the ICER was above the level normally considered an acceptable use of NHS resources. The committee noted that the driver for the ICER being higher in the EAG's base case was using a 50 IU/kg dose of efanesoctocog alfa for treating bleeds.

The committee's preferences

3.24 The committee preferred the model to:

- include emicizumab, SHL (octocog alfa, simoctogog alfa and morcotogog alfa) and EHL (efmoroctocog alfa and, in PTPs only, turoctocog alfa pegol and rurioctocog alfa pegol) factor VIII replacement therapies as relevant comparators for both PTPs and PUPs
- explore alternative approaches to estimating the relative clinical effectiveness of efanesoctocog alfa compared with comparators, including SHL (octocog alfa, simoctogog alfa and morcotogog alfa) and EHL (efmoroctocog alfa and, in PTPs only, turoctocog alfa pegol and rurioctocog alfa pegol) factor VIII replacement therapies
- explore alternative methods of modelling utilities
- explore alternative approaches to modelling wastage
- using an on-demand dose of 50 IU/kg of efanesoctocog alfa for treating bleeds while having prophylaxis.

The committee considered that it could not establish a plausible ICER because of the modelling of relative effectiveness and utilities. It recalled that not all relevant comparators had been included, and there were critical uncertainties in the clinical-effectiveness evidence (ITCs). It considered that the company's and EAG's ICERs were not suitable for decision making. The committee also noted that the modelling did not explore the potential effect of differences in adherence between the clinical trial and NHS populations. This was particularly the case when considering whether adherence would differ for subcutaneous and intravenous administration. So, it thought that the company's model may have overestimated the costs and clinical effectiveness of treatments with poor adherence in clinical practice. The committee concluded that further analyses that addressed the uncertainties and committee's preferences (see sections 3.14 to 3.22 and section 3.24) were needed to establish the cost effectiveness of efanesoctocog alfa.

Other factors

Equality

3.25 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. 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. The committee concluded that all equalities issues for efanesoctocog alfa had been considered in its decision making.

Uncaptured benefits

3.26 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 considered it unlikely that the need for a venous access device for children would decrease as 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 less 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, and considered these as part of its decision making.

Conclusion

Efanesoctocog alfa is not recommended

3.27 The committee noted the important uncertainties in the clinical-effectiveness evidence, and agreed that the inputs in the economic model made it unsuitable for decision making. It also noted that evidence comparing efanesoctocog alfa with all relevant comparators was not available. This meant it was not possible to reliably estimate the cost effectiveness of efanesoctocog alfa. So, it is not recommended. The committee concluded that the company should provide additional information for consideration at the next evaluation committee meeting (see section 3.25).

4 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

Dr 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

Technical adviser

Leena Issa

Project manager

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