National Institute for Health and Care Excellence

Health Technology Evaluation

Efanesoctocog alfa for treating and preventing bleeding episodes in haemophilia A [ID6170]
Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Swedish Orphan Biovitrum, SOBI (company)	Sobi would like to highlight that existing factor and non-factor replacement therapies used in the United Kingdom (UK) for severe haemophilia A have previously been the subject of a national tendering exercise/National Health Service England (NHSE) clinical commissioning policies and did not have to explicitly demonstrate cost-effectiveness. Therefore, efanesoctocog alfa is implicitly being placed at a significant disadvantage due entirely to recent changes in evaluation and commissioning processes. Sobi believe that emicizumab is the most relevant comparator for efanesoctocog alfa. Although it has not been appraised by NICE, it is available for use through the NHS via clinical commissioning policies. [redacted]	Comment noted. This topic has been routed to a Single Technology Appraisal. No action required.
	Novo Nordisk	We have reservations on the appropriateness of evaluating haemophilia treatments through NICE technology appraisals. Considering that all relevant comparators have received reimbursement by NHS Specialised	Comment noted. This topic has been routed to a Single Technology

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		Commissioning and are placed on national frameworks via a tendering process we anticipate equity issues to arise. In addition, historically, there is a paucity of comparative evidence in the haemophilia space and the data that are available are anticipated to not meet NICE's requirements for decision-making.	Appraisal. No action required.
	Octapharma	No comments	Comment noted. No action required.
	Takeda UK	No comment	Comment noted. No action required.
	Royal College of Pathologists	This is new Factor VIII concentrate now with FDA approval with exteded half life requiring once a week dosing only shown to be effective for prophylaxis as well as on demand dosing	Comment noted. No action required.
	United Kingdom Haemophilia Centre Doctors Organisation	This feels reasonable	Comment noted. No action required.
	Genetic Alliance UK	No comment	Comment noted. No action required.
	The Haemophilia Society	Yes, this is the appropriate route.	Comment noted. No action required.
Wording	Swedish Orphan Biovitrum, SOBI (company)	Sobi broadly agrees that the wording is appropriate. However, please see the comments we have provided in later sections, particularly on optimisation of the population and comparators. The draft Summary of Product Characteristics (SmPC) wording for efanesoctocog alfa is as follows:	Comment noted. No action required.

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		[redacted]	
	Novo Nordisk	No comment	Comment noted. No action required.
	Octapharma	No comments	Comment noted. No action required.
	Takeda UK	No comment	Comment noted. No action required.
	Royal College of Pathologists	This should be improved. Currently there exist both standard half-life and extended half-life products which are both efficacious and safe, but lack convenience of once a week dosing except for emicizumab. This could be more clearly explained in the scope	Comment noted. The scope has been updated to acknowledge the administration frequency of injections when used for prophylaxis. The direct and indirect benefits of the intervention versus the comparator will be considered by the committee during the evaluation.
	United Kingdom Haemophilia Centre Doctors Organisation	To appraise the clinical and cost-effectiveness of efanesoctocog alfa within its marketing authorisation for treating and preventing bleeding episodes in people of any age with Haemophilia A without current inhibitor to FVIII.	Comment noted. The remit and population have been kept broad and efanesoctocog alfa will be appraised within its marketing authorisation for treating and preventing

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			bleeding episodes in haemophilia A.
	Genetic Alliance UK	No comment	Comment noted. No action required.
	The Haemophilia Society	The words “with previously treated Haemophilia A” can be omitted. This may have been a requirement in the trial but is unlikely to represent the license conditions. This treatment could and should be an option for people going on to prophylaxis for the first time.	Comment noted. The remit and population have been kept broad and efanesoctocog alfa will be appraised within its marketing authorisation for treating and preventing bleeding episodes in haemophilia A. No action required.
Timing issues	Swedish Orphan Biovitrum, SOBI (company)	Sobi believes an appraisal that allows the publication of guidance shortly after marketing authorisation is obtained would be of value to patients and the NHS.	Comments noted. NICE aims to provide draft guidance to the NHS as close as possible to the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action required.
	Novo Nordisk	No comment	Comment noted. No action required.
	Octapharma	No comments	Comment noted. No action required.

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	Takeda UK	No comment	Comment noted. No action required.
	Royal College of Pathologists	Emicizumab, the comparable product has a monopoly on the market. An alternative product if licences would lead to competion and drive the price of both emicizumab and efanesoctocog alfa down with cost-saving to NHS without compromising ABR and QALY	Comments noted. NICE aims to provide draft guidance to the NHS as close as possible to the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action required.
	United Kingdom Haemophilia Centre Doctors Organisation	We would say 6 to 9 months.	Comments noted. NICE aims to provide draft guidance to the NHS as close as possible to the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action required.
	Genetic Alliance UK	No comment	Comment noted. No action required.
	The Haemophilia Society	There is significant unmet need, particularly for people with severe or moderate haemophilia A as current treatments require frequent dosing and do not maintain factor levels at near-normal levels for long after each treatment.	Comments noted. NICE aims to provide draft guidance to the NHS as close as possible to the date when the

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			marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action required.
Additional comments on the draft remit	Swedish Orphan Biovitrum, SOBI (company)	None	Comment noted. No action required.
	Novo Nordisk	N/A	Comment noted. No action required.
	Octapharma	No comments	Comment noted. No action required.
	Takeda UK	No comment	Comment noted. No action required.
	Royal College of Pathologists	No comment	Comment noted. No action required.
	United Kingdom Haemophilia Centre Doctors Organisation	There is no regulatory requirement for the conduct of studies in previously untreated patients. i.e. PUPs. In young children established on prophylaxis with subcutaenous emicizumab, this is an attractive alternative to standard and extended half-life factor VIII for the management of beeds.	Comment noted. No action required.
	Genetic Alliance UK	No comment	Comment noted. No action required.
	The Haemophilia Society	No comment	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Swedish Orphan Biovitrum, SOBI (company)	Sobi believes the content of the background section is sufficiently accurate. However, it is important to consider that despite relatively low annualised bleed rates, a significant number of unmet needs remain beyond the control of bleeds. Painful joint damage can still occur, particularly when a number of bleeds occur within the same joint and many patients may require a higher factor level throughout the week in the face of a more physical and active lifestyle. Hence, there remains an unmet need for the introduction of more effective treatments that maintain factor VIII levels at near normal levels for the majority of the week.	Comment noted. The committee can consider the unmet need of the condition during the appraisal. No action required.
	Novo Nordisk	No comment	Comment noted. No action required.
	Octapharma	Paragraph 1 The last sentence, "*Females who carry the haemophilia gene may have mild, or, rarely, severe symptoms of bleeding*" – there is no mention of moderate symptoms. Paragraph 2 Provides information on clotting factor levels for mild and moderate haemophilia, but not severe haemophilia. Paragraph 3 The data presented is from the UKHCDO Annual Report (2020/2021) and Reference 2 links to the more recent report (2021/2022). Data in draft requires updating to reflect the current patient population.	Comment noted. The scope has been updated.
	Takeda UK	No comment	Comment noted. No action required.
	Royal College of Pathologists	As mentioned above further clarification is required regarding advantages of efanesoctocog alfa especially in comparison to alternative product	Comment noted. The direct and indirect benefits of the interventions versus the comparator will be considered

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			by the committee during the evaluation. No action required.
	United Kingdom Haemophilia Centre Doctors Organisation	Congenital HA is (always) an inherited disorder.	Comment noted. The background information in the scope has been updated.
	Genetic Alliance UK	It is important to note that living with a chronic, life long condition that currently requires daily injections to manage symptoms can have significant impacts on a person's quality of life. The burden of an individual's treatment may mean that planning outings and overnight trips become more complicated, may prevent some individuals from doing certain activities or they may struggle to adhere to their treatment regime resulting in further complications. It should therefore also be considered that this technology could significantly decrease the burden of treatment as the frequency of administrations would be less than the current treatment options available.	Comment noted. The scope has been updated to acknowledge the administration frequency of injections when used for prophylaxis. Where relevant the direct and indirect benefits of the interventions compared with the comparator will be considered by the committee during the evaluation. .
	The Haemophilia Society	The line "Haemophilia A is normally an inherited condition found in males" is misleading. While severe and moderate haemophilia is rare in women, around 20% of people with mild haemophilia A are women.	Comment noted. The background information in the scope has been updated to clarify.
Population	Swedish Orphan Biovitrum, SOBI (company)	The Phase 3 study investigating in patients aged ≥12 years (XTEND-1) was conducted according to EU regulations for FVIII replacement therapies. Regulators only require efficacy and safety to be demonstrated in a pivotal trial including previously-treated patients with severe haemophilia A (FVIII levels <1 IU/dL). Therefore, the use of	Comment noted. The scope has been updated and has been kept broad. The population includes people with haemophilia A.

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		efanesoctocog alfa in patients with mild/moderate haemophilia A or in untreated patients was not studied. For this reason, Sobi will only be submitting evidence that relates to previously treated patients (PTPs) with severe haemophilia, as reflected in the pivotal XTEND-1 and XTEND-Kids (<12 years) trials. The aim of prophylaxis with replacement therapy for patients with severe haemophilia (FVIII levels <1%) is to prevent haemarthroses and subsequent joint damage (by preventing bleeding into the joints). The majority of patients with severe haemophilia in the UK receive prophylaxis, and it is considered the treatment approach of choice by the UK Haemophilia Centre Directors Organisation (UKHCDO) and World Federation of Haemophilia (1). Traditionally, the aim of prophylaxis was to maintain FVIII levels above 1%. However, there is growing recognition that this is insufficient to prevent bleeding and although variable between patients, much higher FVIII levels between injections are required to prevent bleeding. Indeed, World Federation of Haemophilia guidelines state spontaneous bleeding is uncommon when FVIII levels are >15% (2). Further evidence has shown that FVIII levels >30% resulted in predicted joint bleeding rates of zero (3). While this is difficult to achieve with currently available products, XTEND-1 has demonstrated a mean FVIII activity level of 40% at Day 4, and 15% at Day 7. Thus, patients who receive efanesoctocog alfa are approaching normalised haemostatic levels for the majority of the week, and between injections. On-demand treatment should only be considered within the context of a prophylactic regimen, as an additional requirement following a bleed or as coverage during surgery. In the UK, very few patients with severe haemophilia are treated with on-demand therapy, as it does not prevent bleeding and therefore does not prevent significant joint	

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		damage (the rationale for prophylaxis). A minority of patients with severe haemophilia A who are currently treated with on-demand therapy are thought to be doing so for historical reasons/personal choice, or who have a milder clinical phenotype.	
	Novo Nordisk	No comment	Comment noted. No action required.
	Octapharma	Define further “previously treated”; for example, the treatment type (factor/non-factor), timescale given, and/or is this a minimally treated patient or a previously treated patient who’s received treatment with factor for 150 exposure days?	Comment noted. The scope has been updated and has been kept broad. The population includes people with haemophilia A. The scope also notes that if evidence allows previous treatment will be considered as a subgroup. No action required.
	Takeda UK	Haemophilia A can present with or without inhibitors, there should be clarification on which population this therapy targets.	Comment noted. The scope has been updated and has been kept broad. The population includes people with haemophilia A.
	Royal College of Pathologists	Yes	Comment noted. No action required.
	United Kingdom Haemophilia Centre Doctors Organisation	The word previously treated needs consideration and potential removal.	Comment noted. The scope has been updated and has been kept broad. The population includes people with haemophilia A. The scope also notes that if evidence allows previous treatment will

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			be considered as a subgroup. No action required.
	Genetic Alliance UK	This technology should be an option for people who are starting prophylaxis treatment for the first time, to keep in line with the likely license conditions, therefore the words 'previously treated' can be removed.	Comment noted. The scope has been updated and has been kept broad. The population includes people with haemophilia A. The scope also notes that if evidence allows previous treatment will be considered as a subgroup. No action required.
	The Haemophilia Society	The population could be more simply defined as people with haemophilia A.	Comment noted. The scope has been updated and has been kept broad. The population includes people with haemophilia A. No action required.
Subgroups	Swedish Orphan Biovitrum, SOBI (company)	Sobi does not believe there are definable subgroups that could be considered separately	Comment noted. No action required.
	Novo Nordisk	No comment	Comment noted. No action required.
	Octapharma	Consider any patient on a personalised prophylaxis regime and whether different pharmacokinetics would alter dose/dosing frequency. Consider its use for Immune Tolerance Induction therapy (ITI).	Comment noted. It is not expected that efanesoctocog alfa will be more clinically or cost effective in the subgroups suggested. No action required

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	Takeda UK	No comment	Comment noted. No action required.
	Royal College of Pathologists	More active people with active lifestyle or physically strenuous jobs Patients with inhibitors should be mentioned separately	Comment noted. The scope has been updated and has been kept broad. The population includes people with haemophilia A. The scope also notes that if evidence allows subgroups will be considered based on: severity of haemophilia, presence or development of inhibitors and previous treatment status. No action required.
	United Kingdom Haemophilia Centre Doctors Organisation	A subgroup of children with negative inhibitors but previous inhibitors requires large doses of clotting factor. A switch in these patents is cost and clinically-effective. Many of these children require central access for this intensity of prophylaxis others have very frequent venipunctures. A switch to emicizumab is likely to result in the re-emergence of the inhibitor to FVIII, which can negatively impact the long-term choices available to the patient.	Comment noted. The scope has been updated and has been kept broad. The population includes people with haemophilia A. The scope also notes that if evidence allows subgroups will be considered based on presence or development of inhibitors. No action required.
	Genetic Alliance UK	No comment	Comment noted. No action required.

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	The Haemophilia Society	No comment	Comment noted. No action required.
Comparators	Swedish Orphan Biovitrum, SOBI (company)	Patients with inhibitor levels ≥0.6 BU/ml were excluded from participating in the XTEND-1 and XTEND-Kids trials. Thus, efanesoctocog alfa will not be indicated as a specific treatment for patients who have a current active inhibitor, however, it would still be licensed for patients who may have developed inhibitors in the past. No patients in the XTEND-1 or XTEND-Kids trials developed inhibitors to treatment. However, in line with current practice with existing replacement therapies and UKHCDO clinical guidelines (1), continued use with efanesoctocog alfa would be anticipated if clinically indicated, should a patient receiving it develop an inhibitor. [redacted] Therefore, the most relevant comparator within the appraisal is emicizumab. This also aligns to the study populations in the pivotal XTEND-1 and XTEND-Kids trials, where all patients who switched to efanesoctocog alfa were previously treated with factor replacement therapies.	Comment noted. The scope has been left broad. No action required.

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		The use of emicizumab has, and continues to, rapidly replace the use of existing FVIII products. The 2021/22 UKHCDO annual report clearly indicates there has been a rapid reduction in the use of all brands of FVIII following the introduction of emicizumab (1). It reports a 38.4% reduction in the use of SHL FVIII therapy between 2012/13 and 2021/22; equivalent to 134 million IU. Nearly two-thirds of this percentage reduction occurred between 2020/21 and 2021/22, suggesting their use is continuing to significantly decrease. Indeed, a median of 53% (IQR: 32–64%) of patients within UK treatment centres are now receiving emicizumab in 2021/22, a rise in the median of 14% from 2020/21. This supports the argument of emicizumab is the most relevant comparator within this appraisal.	
	Novo Nordisk	We believe that there is a need to clarify that established clinical management refers to FVIII replacement therapy. Additionally, FVIII treatments are typically not used by patients with inhibitors therefore we do not expect the established clinical management for the population in scope to include treatment for developed inhibitors.	Comment noted. Efanesoctocog alfa will be appraised within its marketing authorisation for treating and preventing bleeding episodes in haemophilia A. The comparators have been updated to specify that established clinical management includes prophylaxis and on-demand factor VIII replacement therapy.
	Octapharma	No comments.	Comment noted. No action required.
	Takeda UK	We consider that Emicizumab should be included in the definition of established clinical management for prophylaxis, and not as a separate standalone comparator. As per the NHS commissioning	Comment noted. The scope has been amended to include emicizumab in established clinical management.

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		guidelines, people with severe haemophilia without inhibitors would be considered for prophylaxis with a choice of Factor VIII or Emicizumab[1]. NHS England. NHS Clinical Commissionign Policy ID 170134P. Available at https://www.england.nhs.uk/wp-content/uploads/2019/08/1819-Emicizumab-as-prophylaxis-in-people-with-severe-congenital-haemophilia-A-without-factor-VIII-inhibitors.pdf (accessed June 2023)	
	Royal College of Pathologists	Yes [defined appropriately]	Comment noted. No action required.
	United Kingdom Haemophilia Centre Doctors Organisation	Agree	Comment noted. No action required.
	Genetic Alliance UK	No comment	Comment noted. No action required.
	The Haemophilia Society	No comment	Comment noted. No action required.
Outcomes	Swedish Orphan Biovitrum, SOBI (company)	Sobi broadly agrees with the listed outcomes. However, we believe 'durability of response to treatment' is better expressed in terms of pharmacokinetic profiles, such as FVIII levels at time points between infusions.	Comment noted. Change in factor VIII levels has been added as an outcome in the final scope.
	Novo Nordisk	We would propose including 'change in factor VIII levels' in the list of relevant outcomes.	Comment noted. The suggested outcome has been added to the scope.
	Octapharma	Consider pharmacokinetic evaluation (for example, clearance mechanism and circulatory parameters).	Comment noted. The scope aims to include the main

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		Consider evaluation of breakthrough bleeds and the efficacy of efanesoctocog alfa: Dosing regimen Is the prescribed dose of 50 IU/kg optimal for all patients to provide sufficient cover without an increased thrombotic risk? Management plan for breakthrough bleeds and safety profile Does the advice to wait at least 72 hours after a dose of efanesoctocog alfa before the next infusion raise concerns about potential factor accumulation or thrombotic risk?	outcomes that are relevant to estimating clinical effectiveness. No action required.
	Takeda UK	We consider that joint bleeds and joint damage should be accounted for in the outcomes (I.e. annualised joint bleed rate). The World Haemophilia Guidelines note in Principle 8 that prophylaxis therapy should prevent recurrent joint and muscle bleeds, reiterated by Principle 12 which notes "The most important indicator of the efficacy of hemostatic therapy is frequency of bleeding, particularly joint and muscle bleeds."[1] Furthermore, guidelines for introduction on prophylaxis for Haem A are based on prevalence of joint bleeds, thereby indicating these should be measured to understand baseline and improvement of joint bleeds after prophylaxis intiation.[2] This is furthered by the UKHCDO guidelines on addressing joint bleeds, which cites that the "early use of prophylaxis can prevent joint bleeding and avoid the cycle of damage associated with recurrent haemarthrosis"[3] 1. Srivastava A, Dolan G, Bagley L, Ozelo MC, Gouider E, Hum D, Pipe SW, Rayner B, Street A, Pierce GF. OF CARE. https://www1.wfh.org/publications/files/pdf-1865.pdf (accessed June 2023)	Comment noted. Joint bleeds will be captured by the outcome 'annualised bleeding rate'. No action required.

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		2. Rayment, Rachel, et al. "Guidelines on the use of prophylactic factor replacement for children and adults with Haemophilia A and B." *British journal of haematology* 190.5 (2020): 684-695. https://doi.org/10.1111/bjh.16704 (accessed June 2023) Hanley, J., et al. "Guidelines for the management of acute joint bleeds and chronic synovitis in haemophilia: a United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) guideline." *Haemophilia* 23.4 (2017): 511-520. DOI: 10.1111/hae.13201 (accessed June 2023)	
	Royal College of Pathologists	Yes [defined appropriately]	Comment noted. No action required.
	United Kingdom Haemophilia Centre Doctors Organisation	• Annualised bleeding rate – agree. • Need for further treatment with FVIII injections – agree • As the treatment is a weekly infusion, we are unsure about the durability of the response; the duration of the response is more appropriate. • The only complication observed in the clinical trial's time frame is the resolution of target joints. Surgeries and the progression of the joint disease require years and not appropriate outcomes. • Adverse effects of treatment – agree. • Health related quality of life – agree • Change in pain • An important measure that patients value is the number of injections in a year. • Duration of factor levels over a week in the normal range, mild and moderate range of severity of Haemophilia.	Comments noted. Change in factor VIII levels has been added as an outcome of interest. The definition of "complications of the disease" has been updated with joint problems and joint surgeries included as examples.
	Genetic Alliance UK	It is important to recognise the impact chronic conditions can have on mental health, education and employment. Some individuals may also	Comment noted. Mental health and pain outcomes will be captured in the 'health-related

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		experience pain that will likely impact all aspects of life. These are not captured in the current list of outcome measures.	quality of life' outcome measure currently listed in the scope. Where relevant the committee may consider aspects that relate to uncaptured benefits and non-health factors. No action required.
	The Haemophilia Society	In addition to the outcomes mentioned NICE should consider pain, mental health impact, joint health score, ability to take part in work, education and social activities, time off work, cost savings in NHS care and social care as well as the burden of treatment.	Comment noted. Mental health and pain outcomes will be captured in the 'health-related quality of life' outcome measure currently listed in the scope. Where relevant the committee may consider aspects that relate to uncaptured benefits and non-health factors. No action required.
Equality	Swedish Orphan Biovitrum, SOBI (company)	Sobi supports the promotion of equality of opportunity. We are unaware of any facets of this appraisal that might impact equality.	Comment noted. No action required.
	Novo Nordisk	No comment	Comment noted. No action required.
	Octapharma	No comments.	Comment noted. No action required.
	Takeda UK	No comment	Comment noted. No action required.
	Royal College of Pathologists	No [equalities issues]	Comment noted. No action required.

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	United Kingdom Haemophilia Centre Doctors Organisation	No comment	Comment noted. No action required.
	Genetic Alliance UK	It is important to ensure that women who are diagnosed with Haemophilia A are not excluded from accessing this technology.	Comment noted. The population in the scope covers all people with haemophilia A. No action required.
	The Haemophilia Society	There are around 15 women and girls with moderate or severe haemophilia A who should not be excluded from accessing this technology. In total there are 850 women diagnosed with haemophilia A in the UK making up over 10% of the eligible population.	Comment noted. The population in the scope covers all people with haemophilia A. No action required.
Other considerations	Swedish Orphan Biovitrum, SOBI (company)	See responses to consultation questions	Comment noted. No action required.
	Novo Nordisk	N/A	Comment noted. No action required.
	Octapharma	Consider impact on national bleeding disorders framework. Consider a cost-economic evaluation for patients experiencing zero bleeds on their current regime.	Comment noted. The committee will make a recommendation based on the available clinical evidence at the time of the evaluation. No action required.
	Takeda UK	No comment	Comment noted. No action required.
	Royal College of Pathologists	Make a stronger case for efanesoctocog alfa	Comment noted. No action required.
	United Kingdom Haemophilia	No comment	Comment noted. No action required.

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	Centre Doctors Organisation		
	Genetic Alliance UK	No comment	Comment noted. No action required.
	The Haemophilia Society	No comment	Comment noted. No action required.
Questions for consultation	Swedish Orphan Biovitrum, SOBI (company)	Are the comparators defined appropriately? Which treatments are considered to be established clinical practice in the NHS for treating or preventing bleeding episodes in people with haemophilia A? [redacted] It is well-established that patients switching from prior factor replacement therapy are most likely to receive emicizumab, and this therefore represents the most appropriate comparator within the appraisal. Are there any relevant subgroups to consider? Beyond the population previously defined above, Sobi does not believe there are definable subgroups that could be considered separately. Where do you consider efanesoctocog alfa will fit into the existing care pathway for the disease? [redacted] How might disease severity and clinical presentation be considered to affect the patient population for which efanesoctocog alfa will be licensed?	Comment noted. Please see responses to previous questions. Where relevant the committee may consider aspects that relate to uncaptured benefits and non-health factors. No action required.

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		See previous comments Would disease severity be considered to affect response to treatment or prophylaxis with efanesoctocog alfa? See previous comments Would efanesoctocog alfa be a candidate for managed access? Sobi considers this to be unlikely. Do you consider that the use of efanesoctocog alfa can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Yes. Sobi appreciates that NICE's preferred outcome measure in economic evaluations is the QALY. However, capturing all aspects of benefit that efanesoctocog alfa provides is challenging. In vivo FVIII levels are clearly related to annualised bleeding rates (ABR), which can be linked to utility losses. However, achieving high sustained FVIII levels is important to patients, as this allows for lifestyles to be more easily tailored to individual requirements. In addition to this, efanesoctocog alfa increases FVIII to normal or near normal levels, where patients experience a non-haemophilia state for the majority of each week; quantifying this additional benefit within a QALY is also difficult. In contrast to emicizumab which generates clotting factor activity equivalent to 10–20% across the week (4), an advantage of efanesoctocog alfa over current factor replacement therapies and emicizumab is that it offers sustained normalised haemostasis by maintaining non-haemophilia levels (FVIII level >40%) for a significant part of the week. This means that FVIII levels are sustained at higher levels across the week, remaining at 15% on Day 7 (5).	

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		While direct evidence to support this benefit could theoretically be collected and incorporated into a QALY estimate, the required study design is impractical. However, as an alternative, Sobi believes inferences can be made about these benefits by examining the pharmacokinetic profiles associated with efanesoctocog alfa and emicizumab, and existing HRQoL evidence for people with mild/moderate haemophilia (i.e. those with FVIII levels between 5 and 40%). Data shows that increasing the time spent with FVIII levels >30% substantially decreases bleeding risk, with implications for the patient's risk of developing arthropathy and long-term complications. Repeated bleeding into a joint breaks down the joint lining and causes irreversible joint damage; this can result in a painful arthritic condition known as haemophilic arthropathy. Arthropathy development, due to sub-optimal haemostatic control, is associated with chronic pain, joint disfigurement, disability & restricted daily life, leading to reduced productivity, societal participation & HRQoL. While all target joints resolved and mean Haemophilia Joint Health Scores improved in XTEND-1 (5), it may not be possible to adequately link these results to the long-term impact on joint health, hence they might not be adequately captured within the QALY estimates. Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. Data from clinical trials is available to demonstrate the pharmacokinetic properties of factor-replacement therapies and emicizumab, showing data on FVIII activity levels. The link between joint health and bleeds is well documented in the clinical literature, however quantifying this relationship remains difficult.	

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	Novo Nordisk	N/A	Comment noted. No action required.
	Octapharma	No comments.	Comment noted. No action required.
	Takeda UK	No comment	Comment noted. No action required.
	Royal College of Pathologists	n/a	Comment noted. No action required.
	United Kingdom Haemophilia Centre Doctors Organisation	*Where do you consider efanesoctocog alfa will fit into the existing care pathway for the disease?* Efa can be used in any patient where standard or extended half-life factors. The outcomes are comparable to Emicizumab and superior to standard and extended half-life factors. In addition, for patients with mild and moderate Haemophilia who cannot self-administer, this will significantly impact clinical effectiveness by decreasing the number of hospital visits or visits by a district nurse. *Would disease severity be considered to affect response to treatment or prophylaxis with efanesoctocog alfa?* It can be used in any patient where replacement therapy with FVIII is indicated. The underlying severity has minimal impact on the efficacy of the treatment. *How might disease severity and clinical presentation be considered to affect the patient population for which efanesoctocog alfa will be licensed?* Clinically it can be used for prophylaxis, mostly in severe and for management of bleeds and targeted prophylaxis in moderate and mild HA patients.	Comment noted. Please see responses to previous questions. Where relevant the committee may consider aspects that relate to uncaptured benefits and non-health factors. No action required.

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		Would efanesoctocog alfa be a candidate for managed access? Yes *Do you consider that the use of efanesoctocog alfa can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?* Response: The treatment burden in Haemophilia is underestimated. We draw attention to the long-established concept of the 'disability paradox', where patients typically report greater happiness and QoL across a wide range of health conditions than healthy people under similar circumstances (Albrecht and Devlieger 1999). This phenomenon is more marked in patients with inherited disorders because they do not have a normal baseline for comparison. It has been particularly challenging to assess the change in treatment burden, as no validated tool exists. Patients with chronic health conditions often undertake risk-benefit analyses about their treatment adherence. They can actively decide not to follow the recommendations because of time and other considerations, i.e. rationalised or reasoned non-adherence (Demain, Goncalves et al. 2015). Quality of life instruments are not particularly sensitive, and clinical experience suggests that they fail to capture significant benefits to patients that derive from reduced treatment burden and changes towards a new and more active life relatively unburdened by disease. *Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.* Structured Interviews with people with Haemophilia A who have received this treatment will be beneficial.	

Section	Consultee/ Commentator	Comments [sic]	Action
	Genetic Alliance UK	No comment	Comment noted. No action required.
	The Haemophilia Society	No comment	Comment noted. No action required.
Additional comments on the draft scope	Swedish Orphan Biovitrum, SOBI (company)	None	Comment noted. No action required.
	Novo Nordisk	NHS England. Clinical Commissioning Policy: Emicizumab as prophylaxis in people with congenital haemophilia A with factor VIII inhibitors (all ages). 170067/P. July 2018: We propose removing the above policy from the list of related national policies given that FVIII treatments are typically not offered to people with factor VIII inhibitors.	Comment noted. Efanesoctocog alfa will be appraised within its marketing authorisation for treating and preventing bleeding episodes in haemophilia A. No action required.
	Octapharma	Consider evaluation of immunogenicity. There is no data available on the clearance mechanism of efanesoctocog alfa. Could accumulation of the XTEN polymer or D'D3 dimer, or of endogenous VWF, be a concern? There is evidence that FVIII has roles beyond haemostasis. For example, the FVIII-von Willebrand factor complex inhibits osteoclastogenesis and therefore impacts bone metabolism. Given that efanesoctocog alfa doesn't bind endogenous VWF, will efanesoctocog alfa be able to replace the action of FVIII in such roles?	Comment noted. The committee will make a recommendation based on the available clinical evidence at the time of the evaluation. No action required.
	Takeda UK	No comment	Comment noted. No action required.
	Royal College of Pathologists	The arrival of an alternative product with once weekly dosing is welcome	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	United Kingdom Haemophilia Centre Doctors Organisation	No comment	Comment noted. No action required.
	Genetic Alliance UK	No comment	Comment noted. No action required.
	The Haemophilia Society	No comment	Comment noted. No action required.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

None