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Clinical evidence review of susoctocog alfa for treating bleeding episodes in people with acquired haemophilia A

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About this clinical evidence review

Clinical evidence reviews provide a summary of the best available evidence for a single technology within a licensed indication that falls under the remit of NHS England’s specialised commissioning for which the responsible commissioner is NHS England. The clinical evidence review supports NHS England in producing clinical policies but is not NICE guidance or advice.
Summary

Acquired haemophilia A (AHA) is a rare bleeding disorder that occurs when the body produces autoantibodies to factor VIII, a protein involved in blood clotting. The reduction in factor VIII caused by the autoantibodies is associated with an increased risk of bleeding, which may be spontaneous or in response to often minimal trauma or surgery.

Susoctocog alfa (Obizur) is a purified, recombinant porcine factor VIII, which has a UK marketing authorisation for treating bleeding episodes in adults with AHA. It is made by genetic engineering using a section of the factor VIII gene from pigs.

The main evidence for the safety and efficacy of susoctocog alfa is an uncontrolled, prospective, open-label study in people with AHA (Kruse-Jarres et al. 2015). In the study, 28 participants (100%) who experienced a serious bleeding event had a ‘positive response’ to susoctocog alfa 24 hours after starting treatment.

After the final infusion of susoctocog alfa, bleeding was successfully controlled in 24/28 participants (85.7%). Overall control of bleeding episodes was not achieved in 4 people, although they had a positive response to treatment at the 24-hour assessment. These people were later withdrawn from the study because, for example, subsequent bleeds were not successfully controlled or medical complications occurred.

No evidence was found for using susoctocog alfa in subgroups of people with AHA who cannot be treated with a bypassing agent, for example, because they are at high risk of thromboembolism. Since susoctocog alfa was launched in 2015, several retrospective case series (Tarantino et al. 2017, n=7; Martin et al. 2016, n=4; and Stemberger et al. 2016, n=2) have reported limited experience of using a lower loading dose (100 units/kg) of susoctocog alfa in people with AHA and bleeding episodes to reduce the risk of thromboembolism. Bypassing agents had previously been tried unsuccessfully by 11/13 cases (85%) described. Across the case series, bleeding responded to susoctocog alfa in 10/12 people who received the lower loading dose. The
other 2 people died. Case series provide lower quality evidence than the prospective study by Kruse-Jarres et al. (2015) and should be interpreted with caution.

No evidence was found for using susoctocog alfa to treat bleeding episodes in women with AHA who are pregnant or breastfeeding. The summary of product characteristics states that susoctocog alfa should be used during pregnancy and breastfeeding only if it is clearly indicated.

The European public assessment report for susoctocog alfa states that it is not fully known how people will respond immunologically to a second exposure to susoctocog alfa, although some people in the study by Kruse-Jarres et al. (2015) were treated for second episodes of bleeding, apparently with no concerns.

The European public assessment report for susoctocog alfa states that further data on the clinical efficacy and safety of susoctocog alfa for treating bleeding episodes in people with AHA will be provided through a surveillance programme and registry, and a prospective non-interventional study. The company was also advised to continue validation of the one-stage clotting assay, which is used to measure factor VIII activity.
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### Abbreviations and medical terms

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<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>aPCC</td>
<td>Activated prothrombin complex concentrate, a bypassing agent for managing bleeding in people with AHA</td>
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<tr>
<td>AHA</td>
<td>Acquired haemophilia A, a rare autoimmune disorder caused by autoantibodies to factor VIII, characterised by bleeding</td>
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<tr>
<td>BU</td>
<td>Bethesda units, a measure of the concentration of factor VIII in the body</td>
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<tr>
<td>pd-pFVIII</td>
<td>Plasma-derived porcine factor VIII, a treatment made from the purified plasma of pigs, which was withdrawn in 2004 due to safety concerns</td>
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<tr>
<td>pFVIII</td>
<td>Porcine factor VIII, either plasma-derived or recombinant</td>
</tr>
<tr>
<td>rFVIIa</td>
<td>Activated recombinant factor VII, a bypassing agent for managing bleeding in people with AHA</td>
</tr>
<tr>
<td>rpFVIII</td>
<td>Recombinant porcine factor VIII, susoctocog alfa, the subject of this evidence review</td>
</tr>
<tr>
<td>hFVIII</td>
<td>Human factor VIII</td>
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<tr>
<td>Medical term</td>
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<tr>
<td>Acquired haemophilia A</td>
<td>A rare bleeding disorder that occurs when the body produces autoantibodies to factor VIII, a protein involved in blood clotting</td>
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<tr>
<td>Antibody</td>
<td>A type of protein produced by the body’s immune system, which combines with foreign material in the body (such as bacteria or viruses) to act against it</td>
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<tr>
<td>Autoantibody</td>
<td>An antibody that acts against the body’s own tissues</td>
</tr>
<tr>
<td>Autoimmune disease</td>
<td>A disease in which the body’s immune system acts against its own healthy cells and tissues</td>
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<tr>
<td>Bethesda units</td>
<td>The Bethesda assay is used to quantify the concentration of factor VIII inhibitor. One Bethesda unit (BU) is the amount of inhibitor required to neutralise 50% of a unit of factor VIII in normal plasma after incubation at 37°C for 2 hours</td>
</tr>
<tr>
<td>Factor VIII</td>
<td>A protein involved in blood clotting</td>
</tr>
<tr>
<td>Fibrin</td>
<td>An insoluble protein formed from fibrinogen during the blood clotting process. It forms a fibrous mesh that impedes the flow of blood</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>A soluble protein present in blood plasma, from which fibrin is produced by the action of the enzyme thrombin</td>
</tr>
<tr>
<td>Infusion</td>
<td>A method of injecting fluids, including medicines, into the bloodstream</td>
</tr>
<tr>
<td>Intravenous</td>
<td>Into a blood vein</td>
</tr>
<tr>
<td>Prothrombin</td>
<td>A protein present in blood plasma, which is converted into thrombin during the blood clotting process</td>
</tr>
<tr>
<td>Recombinant</td>
<td>Recombinant material (such as genes, proteins or cells) is formed by genetic engineering, by combining genetic material from more than 1 place. Susoctocog alfa is a recombinant protein that is genetically engineered using the factor VIII gene from pigs</td>
</tr>
<tr>
<td>Thrombin</td>
<td>An enzyme in blood plasma, which causes the clotting of blood by converting fibrinogen to fibrin</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>This occurs when a blood clot (thrombus) in a blood vessel is dislodged and carried by the blood stream until it blocks another blood vessel</td>
</tr>
<tr>
<td>Titre</td>
<td>The concentration of a substance (such as an antibody) in solution, which is worked out by a method called titration</td>
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Introduction

Disease Background

Acquired haemophilia A (AHA) is a rare bleeding disorder that occurs when the body produces autoantibodies to factor VIII, a protein involved in blood clotting. About half of cases are associated with a condition such as malignancy, autoimmune disease or pregnancy, or present as an adverse reaction to a medicine. Other cases have no known cause (European public assessment report for susoctocog alfa).

The reduction in factor VIII caused by the autoantibodies is associated with an increased risk of bleeding, which may be spontaneous or in response to often minimal trauma or surgery. The pattern of bleeding in people with AHA differs from that seen in people with the more common congenital haemophilia. Bleeding most often occurs into skin and soft tissues, and people with AHA may present with, for example, compartment syndrome, haematuria, gastrointestinal bleeding and prolonged post-partum bleeding. Bleeding may be life or limb-threatening; the reported mortality rate for AHA is up to 20%. Therefore, people with AHA who present with bleeding are in need of urgent, specialist attention (European public assessment report for susoctocog alfa).

Focus of review

In line with the anticipated marketing authorisation, the focus of this review is on susoctocog alfa for treating bleeding episodes in adults with AHA.

Epidemiology and needs assessment

AHA has an incidence of about 1.5 per million/year and presents most commonly in older people with a median age of 75–80 years. It is a rare complication of pregnancy, reported in 1 in 350,000 births in the UK (UK Haemophilia Centres Doctors’ Organisation [UKHCDO] Guideline on diagnosis and management of acquired coagulation inhibitors, 2013).

The UK National haemophilia database has Bleeding disorder statistics for April 2015 to March 2016. This shows that 106 new people with AHA were
added to the register during that period. In total, 475 people (236 male and 239 female) with AHA were on the register between those dates, 102 of whom were treated (21.4%).

**Product overview**

**Mode of action**

A series of complex reactions occur in the body to produce blood clots and stop bleeding (the coagulation cascade). Factor VIII helps to produce activated factor X, which ultimately converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin so that clots can form. In people with AHA, autoantibodies neutralise human factor VIII, preventing this process and inhibiting blood clotting (Summary of product characteristics for susoctocog alfa).

Susoctocog alfa (Obizur) is a recombinant, porcine factor VIII (rpFVIII) that, on infusion, temporarily replaces the human factor VIII, thereby improving blood clotting and reducing bleeding in people with AHA. The autoantibodies against human factor VIII have little or no effect on susoctocog alfa (Summary of product characteristics for susoctocog alfa).

**Regulatory status**

Susoctocog alfa received a marketing authorisation in November 2015. It is licensed for treating bleeding episodes in adults with AHA (Summary of product characteristics for susoctocog alfa).

**Dosing information**

Susoctocog alfa is available as a powder (500 units/vial) and solvent for solution for infusion. Treatment should be under the supervision of a doctor experienced in the treatment of haemophilia, on an inpatient basis only. The bleeding status of the person requires clinical supervision (Summary of product characteristics for susoctocog alfa).

The dose, frequency and duration of treatment with susoctocog alfa depend on the location, extent and severity of the bleeding episode, target factor VIII
activity, and the person’s clinical condition (Summary of product characteristics for susoctocog alfa).

The recommended initial loading dose is 200 units/kg bodyweight by intravenous (IV) infusion. For example, for a 70 kg person, the initial dose will be 14,000 units; 28 vials will be required for this dose. The person’s factor VIII activity and clinical condition should be monitored 30 minutes after the first infusion and 3 hours later. The one-stage clotting assay for factor VIII is recommended because it has been used to determine the potency of susoctocog alfa and the mean recovery rate (Summary of product characteristics for susoctocog alfa); however, the chromogenic assay may also be used.

Subsequent doses and frequency of administration (4–12 hourly) should be based on clinical response and results of factor VIII activity monitoring. Factor VIII activity should be monitored before and 30 minutes after each dose, and be maintained within recommended limits (Summary of product characteristics for susoctocog alfa). A clinical study in 28 people (Kruse-Jarres et al. 2015) found that subsequent doses were lower than the loading dose (median 100 units/kg, see the results tables for more information).

The summary of product characteristics gives recommended target factor VIII trough levels for the initial phase (depending on the type and severity of bleeding) and for the healing phase, once bleeding has responded (usually within 24 hours). The length of treatment depends on clinical judgement.

**Treatment pathway and current practice**

The aims of treating people with AHA are, firstly, to stop the acute bleed and, secondly, to suppress autoantibody formation. When treatment for bleeding is required, human factor VIII cannot be used in people with AHA, even at high doses, because it is rapidly inactivated by the factor VIII autoantibodies. Therefore, a different type of clotting factor that does not rely on factor VIII may be used. These treatments are called ‘bypassing agents’ because they work on different parts of the clotting process to ‘bypass’ the effect of the factor VIII inhibitor. They include activated prothrombin complex concentrate.
(aPCC, FEIBA, which contains various inactivated or activated clotting factors) and activated recombinant factor VII (rFVIIa, eptacog alfa, NovoSeven).

Response to bypassing agents is assessed on clinical grounds because no suitable laboratory tests are currently available. This may be difficult where bleeding is concealed inside an internal organ or body cavity (European public assessment report for susoctocog alfa); for example, bleeding inside the brain.

As might be expected with any treatment that causes blood to clot, there are published case reports of venous and arterial thrombosis associated with bypassing agents, (which must be considered when treating people with AHA who may be high-risk because of their age and comorbidities). Exposure to aPCC, which contains factor VIII, may also lead to an increase in the concentration of autoantibodies in the recipient (European public assessment report for susoctocog alfa).

The UKHCDO Guideline on diagnosis and management of acquired coagulation inhibitors (which was published in 2013 and does not include susoctocog) includes the following evidence-based recommendations on treating bleeding in people with AHA:

- If indicated, bleeding should be treated without delay using rFVIIa or aPCC (grade 1B). Not all bleeds need treating and many subcutaneous bleeds can be managed conservatively. If the initial bypassing agent is ineffective, the other should be tried at an early stage (grade 2C)
- The use of high doses of rFVIIa is not recommended except as rescue therapy because of the increased risk of thrombosis (grade 2C)
- Factor VIII replacement combined with plasmapheresis and immunoadsorption can be considered for severe bleeding or if first-line therapy is unsuccessful (grade 2B)
- Tranexamic acid should be considered for all bleeds and especially those involving mucosal surfaces (grade 2C)
- Once in remission, people should be assessed for the risk of venous thrombosis and given prophylaxis if indicated (grade 2C).
Of 102 people with AHA who were treated between April 2015 and March 2016, aPCC was used to treat 88 people and rFVIIa was used to treat 29 people (Bleeding disorder statistics for April 2015 to March 2016). Some people were treated with both products.

Immunosuppressants (such as corticosteroids and cyclophosphamide) are used to eradicate factor VIII autoantibodies and are effective in up to 70% of people (European public assessment report for susoctocog alfa). However, it may be several weeks before autoantibody levels fall and factor VIII levels increase. During this period, bleeds need to be stopped and the risk of further bleeding should be minimised. Autoantibodies recur in about 1 in 5 cases after a median of 7.5 months, and some people need to take long-term immunosuppressants (UKHCDO Guideline on diagnosis and management of acquired coagulation inhibitors). See the UKHCDO guideline for more details on treatment options for eradicating autoantibodies.

Plasma-derived porcine factor VIII (pd-pFVIII, Hyate:C, purified from the plasma of pigs) was used to treat severe bleeding episodes in people with haemophilia and antibodies to human clotting factor VIII from 1984 to 2004. However, it was withdrawn due to concerns about the safety of exposing humans to porcine infections (European public assessment report for susoctocog alfa).

**Evidence base**

A literature search was undertaken, which identified 242 references (see appendix 1 for search strategy). These references were screened using their titles and abstracts, and 7 full text references were obtained and assessed for relevance. Full text inclusion and exclusion criteria were applied to the identified studies and 1 study was included in the clinical evidence review (see appendix 2 for inclusion criteria and a list of studies excluded at full text with reasons).

The company submission identified 2 published papers. Both of these had already been identified in the literature search. The company also provided
details of an unpublished study, but the publication date is not yet confirmed and this study has not been included.

Clinical evidence

Overview of included studies

The main evidence for the efficacy and safety of susoctocog alfa is an uncontrolled prospective open-label phase II/III study in people with AHA (Kruse-Jarres et al. 2015, n=29). This study was considered by the European Medicines Agency during the regulatory process (European public assessment report for susoctocog alfa).

A summary of the characteristics of the included study is shown in table 1 (see evidence tables for full details).

Table 1 Summary of included study

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention and comparison</th>
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<tbody>
<tr>
<td>Kruse-Jarres et al. 2015</td>
<td>29 adults* (median age 70 years) with AHA and a serious bleed (for example, a bleed that threatened vital organ function or required a blood transfusion) 1 person was later shown not to have factor VIII autoantibodies and was not included in efficacy analyses A washout period was required if aPCC or rFVIIa were previously used (10 participants)</td>
<td>Evaluated the efficacy and safety of susoctocog alfa for treating serious bleeds The loading dose was 200 units/kg bodyweight Subsequent doses were based on clinical response and factor VIII activity levels No comparator was used</td>
</tr>
</tbody>
</table>

Key outcomes

The key outcomes identified in the scope are discussed below for effectiveness and safety. Table 2 in this section provides a grade of evidence summary of key outcomes (see appendix 5 for the details of grading)
evidence). The more detailed evidence tables and results for each study can be found in appendices 3 and 4.

Effectiveness

Proportion of serious bleeding episodes that responded

In the study by Kruse-Jarres et al. (2015), all 28 participants (100% of people who had factor VIII antibodies) with AHA and a serious bleed had a 'positive response' to treatment 24 hours after initiation of susoctocog alfa (the primary outcome). A 'positive response' was defined as 'effective' or 'partially effective' control of bleeding, as determined by the investigator using a rating scale. It is unclear whether this rating scale has been validated.

Response to treatment was also assessed at 8 hours and 16 hours, although not all participants were assessed at all time-points. At 8 hours 19/20 participants (95%) had a positive response to treatment with susoctocog alfa. At 16 hours, 18/18 (100%) had a positive response to treatment.

Proportion of serious bleeding episodes controlled at the final dose

In the study, overall treatment success or failure was assessed by the investigator using a checklist of anticipated sites of bleeding at the time of the final infusion of susoctocog alfa (median 7 days, range 1–25 days). At that time bleeding was successfully controlled in 24/28 participants (85.7%).

Four participants were withdrawn from the study and, although a positive response to treatment was seen at the 24-hour assessment, overall control of bleeding at the end of the study was not assessed as successful. One person, whose primary bleed was controlled, discontinued susoctocog because it was ineffective for controlling a third bleed. Another person was withdrawn from medical support by family; another experienced sepsis following a procedure, after 4 bleeds were treated successfully; and the final person discontinued treatment because they developed antibodies against susoctocog (anti-pFVIII antibodies) after the primary bleed was controlled.
In participants treated with susoctocog alfa first-line, bleeding was successfully controlled in 16/17 (94%) after a median 7 days (range 1–25 days). For comparison, bleeding was successfully controlled in 8/11 participants (73%) who had been treated with a bypassing agent (n=10 [7 rFVIIa and 3 aPCC]) and/or tranexamic acid (n=3) before receiving susoctocog alfa.

**Dose, number and frequency of infusions in the first 24 hours**

In the 24 participants whose bleed was successfully controlled, Kruse-Jarres et al. (2015) found that the median total dose of susoctocog alfa administered in the first 24 hours of treatment was 485.7 units/kg (range 100–2,100 units/kg). The median individual dose was 200.0 units/kg (range 88–400 units/kg), with a median 3.5 infusions (range 1–7 infusions) administered at a median interval of 7.4 hours (range 3–23 hours).

**Dose, number and frequency of infusions throughout the study**

In the 24 participants whose bleeding was successfully controlled, the median individual dose after the first 24 hours was lower than the median individual dose in the first 24 hours (100.0 units/kg [range 34–400 units/kg] compared with 200.0 units/kg [range 88–400 units/kg] respectively).

When overall exposure to susoctocog alfa was considered, the frequency, dose and number of infusions required to successfully control bleeding varied widely across the 29 participants who received treatment. The median total dose was 1,637.0 units/kg (range 100–20,660 units/kg) and the median individual dose was 133.0 units/kg (range 34–400 units/kg). A median 13.0 infusions (range 1–140 infusions) were administered over a median 7.0 days (range 1–25 days).

**Factor VIII activity levels**

The median increase in factor VIII activity levels after the loading dose was 203% in all 29 participants exposed to treatment in the study.

The increase was lower in 10 participants with anti-pFVIII antibodies, which act against susoctocog: median 96% (range 73–203%) in 6 participants with a
low antibody titre (0.8–4 Bethesda units [BU/ml]) and 29% (range 20–68%) in 4 participants with a high antibody titre (10–29 BU/ml). With repeated dosing, all 10 participants achieved a rise above 100% after 24 hours, and all had a positive response to treatment after 24 hours.

Fosbury et al. (2017) assessed the study data and considered the impact of anti-pFVIII antibodies on participants’ recovery. They concluded that the presence of anti-pFVIII antibodies had an impact on recovery and identified 3 groups of people:

- those with no anti-pFVIII antibodies (n=18) who generally needed lower doses of susoctocog alfa in the first 24 hours, with longer intervals between infusions, and whose factor VIII levels often became supraphysiological (higher than would be seen naturally in the body) after treatment,
- those with anti-pFVIII titres of less than 5 BU/ml (n=6) whose outcomes were considered to be ‘near-normal’, and
- those with higher anti-pFVIII titres of at least 10 BU/ml (n=4) who generally needed higher doses of susoctocog alfa and more frequent infusions in the first 24 hours, and whose post-treatment factor VIII levels were usually lower than in the other groups.

Fosbury et al. (2017) stated that increased treatment intensity (such as that seen in people with high antibody titres above 10 BU/ml) increases cost of care, with potential for treatment failure. They proposed a treatment algorithm that takes into account the availability of factor VIII and anti-pFVIII antibody testing (particularly baseline antibody titres), and the severity of bleeding.

Note that people with a high anti-pFVIII antibody titre of more than 20 BU/ml were excluded from the study (apart from 1 person with a titre of 29 BU/ml who responded to susoctocog alfa before the titre was available and was subsequently allowed to continue treatment). Also, the number of people in 2 of the groups is small (n=4 and n=6).
Grade of evidence and limitations of the evidence

The grade of evidence for all of the outcomes described above is grade C (1 study scoring 4–6/10 points, which is directly applicable).

It is difficult to undertake clinical trials in rare diseases such as AHA because of the small number of eligible participants who are spread across a wide geographical area. The main evidence for susoctocog alfa comes from the uncontrolled open-label observational study by study Kruse-Jarres et al. (2015), which is of low-quality and has many limitations that affect its application to clinical practice. Observational studies have limitations inherent in their non-randomised design, especially around bias and confounding (including demographic and environmental factors, duration of disease and comorbidities). In this study, outcome assessment was not blinded, which is another potential source of bias. The study included only 29 people, which limits its ability to detect rare adverse effects of treatment.

The European public assessment report for susoctocog alfa states that the design of the study by Kruse-Jarres et al. (2015) and use of clinical judgement (rather than an objective measurement) to assess the primary endpoint (albeit coupled to a rating scale) are known to be susceptible to bias. However, it notes that the design and conduct of the study are acceptable because of the rarity of AHA and the emergency nature of the bleeding, and that Scientific advice from the Committee for Medicinal Products for Human Use was followed. The report also states that the magnitude of the effect seen with susoctocog alfa is reassuring. It notes that the participants were mostly older people with extensive clinical histories who were treated in specialist centres for haemophilia, and the population was representative of the European population with AHA.

The European public assessment report states that the marketing authorisation was granted under exceptional circumstances based on this study, subject to the company collecting and analysing immediate and long-term data on clinical efficacy and safety in all people with AHA who are treated with susoctocog alfa.
Safety and tolerability

Seven deaths occurred during the study by Kruse-Jarres et al. (2015). These included 3 bleeds, but none were considered by the investigators to be related to study treatment or to be due to failure of treatment. No serious treatment-related adverse events were seen. Five people developed anti-pFVIII antibodies during treatment. Bleeding was not controlled in 2 of these people.

The European public assessment report for susoctocog alfa reports that 264 treatment-emergent adverse events were reported by 27/29 (93%) participants in the study by Kruse-Jarres et al. (2015). Most were mild (50.4%) or moderate (37.9%) in severity, and only 7 were considered by the investigator to be related to susoctocog alfa. Apart from development of anti-pFVIII antibodies, these were subsequently considered unrelated to treatment.

The summary of product characteristics for susoctocog alfa advises that hypersensitivity or allergic reactions are possible and may progress to severe anaphylaxis. Between 1 in 10 and 1 in 100 people with AHA may develop inhibitory antibodies to pFVIII. High and sustained factor VIII activity in blood may predispose to thromboembolic events, and older people and those with pre-existing cardiovascular disease are particularly at risk. Therefore, treatment should be tailored to achieve recommended factor VIII levels. The risk of catheter-related complications such as catheter site thrombosis should also be considered.

An additional potential risk identified in the European public assessment report for susoctocog alfa includes dose dispensing errors. The report raised concerns that the large number of vials needed per infusion or per day may lead to mistakes in the dosage administered. Although the formulation of susoctocog alfa has been changed and the number of vials required has been reduced since the report was published, the loading dose for a 70 kg person requires 28 vials.
Evidence gaps

People at high risk of thromboembolism

No evidence was found for using susoctocog alfa in subgroups of people with AHA who cannot be treated with a bypassing agent, for example, because they are at high risk of thromboembolism. No cases of thromboembolism were seen in the study by Kruse-Jarres et al. (2015). However, concerns have been raised because supraphysiological factor VIII levels (higher levels than would be seen naturally in the body) were seen with the 200 units/kg loading dose in the study, increasing the risk of thromboembolic events. In the study, peak factor VIII activity levels varied widely in participants in the first 24 hours following a loading dose of 200 units/kg (20–540% immediately post-dose, highest level in the first 24 hours 160–775%). The European public assessment report for susoctocog alfa states that this suggests it may be necessary to give a standard loading dose in order to ensure that everyone reaches sufficient levels of factor VIII activity to treat the bleeding episode. This will lead to overdosing in some people; however, in the life-threatening emergency situation of initial presentation with bleeding, individual dose titration will not be possible.

Evidence for using lower doses of susoctocog alfa in people at risk of thromboembolism

Since susoctocog alfa was launched in 2015, several retrospective case series (Tarantino et al. 2017, n=7; Martin et al. 2016, n=4; and Stemberger et al. 2016, n=2) have reported limited experience of using a lower loading dose (100 units/kg) to reduce the risk of thromboembolism in people with AHA and bleeds.

The case series by Tarantino et al. 2017 included 7 people (mean age 68.3 years) with AHA who received susoctocog alfa for a bleed after other treatments had limited efficacy. Of these, 6 people received a loading dose of 100 units/kg and 1 person received 200 units/kg. Subsequent doses ranged from 30–200 units/kg (median 30–100 units/kg). Treatment decisions were
based on clinical response and factor VIII activity levels. Six people took immunosuppressant treatments.

Bleeding resolved within a few hours of susoctocog alfa being administered in the person who received the standard loading dose. In those who received a reduced loading dose, bleeding resolved within 24–48 hours in 3 people and within 4 days in 1 person. Bleeding did not resolve with treatment in the other 2 people, who subsequently died. Factor VIII activity increased from <1–9% to 109–650% within 0.25–7 hours of treatment initiation in all but 1 person. Human factor VIII (hFVIII) antibody levels were substantially raised at baseline in the 2 people whose bleeding did not resolve with susoctocog alfa, which may have been because of cross-reactivity to pFVIII. Repeated anti-pFVIII antibody testing was only undertaken in 1 person whose initial bleed resolved within 24 hours but required increasing doses of susoctocog alfa, probably because of raised anti-pFVIII and anti-hFVIII antibody titres.

The mean total dose of susoctocog alfa was 1,230 units/kg, administered using a mean 21 infusions, over a mean 14 days. Across the cases, there was considerable variability in the dosing of susoctocog alfa, immunosuppressive therapy and laboratory monitoring. No treatment-related adverse events were seen.

Martin et al. 2016 reported experience of treating 4 people (median age 67.5 years) with AHA for 13 bleeding episodes using a loading dose of 100 units/kg susoctocog alfa. Dosages and treatment intervals were then adjusted based on peak and trough levels of factor VIII until bleeding improved. Three people had previously received rFVIIa. The fourth person had systemic arteriovascular disease and did not receive a bypassing agent. All received immunosuppressant therapy.

All 4 people experienced clinical improvement of bleeding within 12–24 hours of initiation of susoctocog alfa. The mean peak plasma factor VIII level at 20–90 minutes after the initial dose was 134% (SD 33%, range 94–183%). Three people had detectable anti-pFVIII antibodies at baseline, which increased after initiation of susoctocog alfa in 2 (levels were not rechecked in the other
person, who was treated for 1 bleed only). The fourth person developed anti-pFVIII antibodies. In 2 people, treatment continued to be effective over several bleeds but, in another person, anti-pFVIII increased over time until susoctocog alfa was ineffective.

The overall mean dose of susoctocog alfa was 51.2 units/kg (SD 16.5 units/kg) and the average number of infusions needed to control a bleeding episode was 13.2 (SD 10.5), over an average of 4 days (SD 2.1 days). For 10/13 bleeds, the dosing interval was reduced from 4 hourly to 6–12 hourly.

One person developed a deep vein thrombosis (DVT) 10 days after the 45th dose of susoctocog alfa. Their peak plasma factor VIII was 193%, 12 days before the onset of symptoms of DVT. No other adverse effects were reported.

Stemberger et al. 2016 described 2 cases (aged 77 years and 78 years) with AHA and life-threatening bleeding despite treatment with bypassing agents, who received a reduced loading dose of susoctocog alfa 100 units/kg because of an increased thromboembolic risk. The dose was subsequently adjusted based on factor VIII activity levels (to maintain trough levels of factor VIII over 80%) and clinical response. Both cases also received immunosuppressant treatments.

In the first person, after the first infusion the factor VIII activity level was 118%. Bleeding decreased and the clinical condition of the person improved within 24 hours. The dose of susoctocog alfa was maintained at 100 units/kg 8 hourly and bleeding stopped. Treatment was continued for 12 days. In the second person, post-infusion factor VIII was 139% after the first dose. Susoctocog alfa was administered for 12 days, initially at a dose of 50 units/kg 12 hourly, which was then gradually reduced. No thrombotic events were experienced by either person, and no increases in pre-existing antibodies to hFVIII and pFVIII were seen.

Retrospective case series are subject to bias and confounding, limiting their generalisability to wider populations. Higher-quality evidence is required to
compare the efficacy and safety of reduced and standard loading doses of susoctocog alfa.

**Other groups of people for whom there is limited evidence for using susoctocog**

No evidence was found for using susoctocog alfa to treat bleeding in women with AHA who are pregnant or breastfeeding. The *summary of product characteristics* states that susoctocog alfa should be used during pregnancy and lactation only if clearly indicated. There is also little data on using bypassing agents in pregnant or breastfeeding women.

The European public assessment report for susoctocog alfa states that it is not fully known how people will respond immunologically to a second exposure to susoctocog alfa, although some people in the study by Kruse-Jarres et al. (2015) were treated for second episodes of bleeding, apparently with no concerns. Some people in the case series were also treated for more than 1 bleed.

**Monitoring response to susoctocog**

**Factor VIII**

The *summary of product characteristics for susoctocog alfa* recommends the one-stage clotting assay for monitoring response to treatment because it has been used in determination of the potency and the mean recovery rate of susoctocog alfa. The European public assessment report for susoctocog alfa states that the company was advised to continue validation of the one-stage clotting assay for monitoring factor VIII activity.

In the UK the chromogenic and one-stage clotting assays are widely available. Factor VIII activity determined by the chromogenic assay is generally lower than factor VIII activity determined by the one-stage clotting assay. Therefore, the summary of product characteristics advises that measurement of factor VIII activity must always be carried out using the same assay in an individual person.
**Anti-pFVIII antibodies**

According to the summary of product characteristics for susoctocog, in the study, anti-pFVIII antibodies were measured using a modification of the Nijmegen variation of the Bethesda assay, and were detected before and after exposure to the medicine. The summary of product characteristics recommends that treatment should be based on clinical judgement and not based on detection of inhibitory antibodies by the Bethesda assay because people with inhibitor titres of up to 29 BU saw a positive response to treatment. However, Fosbury et al. (2017) found that people with antibody titres of more than 10 BU generally needed higher doses of susoctocog alfa and more frequent infusions in the first 24 hours. They considered that the burden of treatment with susoctocog alfa may be high and present logistical challenges in people with high antibody titres, which may affect the choice of treatment.

The Nijmegen variation of the Bethesda assay may help to inform choice of treatment, and monitor the effects of treatment. However, this assay is not currently widely available in the UK, and the optimal monitoring schedule is not known.
<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Study</th>
<th>Critical appraisal score</th>
<th>Applicability</th>
<th>Grade of evidence</th>
<th>Results</th>
<th>Interpretation of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of serious bleeding episodes that responded to treatment</td>
<td>Kruse-Jarres et al. 2015</td>
<td>5/10</td>
<td>Directly applicable</td>
<td>C</td>
<td>24 hours after initiation of treatment: 28/28 (100%, 95% confidence interval 88.1% to 100%)&lt;br&gt;8 hours after initiation of treatment: 19/20 (95%)&lt;br&gt;16 hours after initiation of treatment: 18/18 (100%)</td>
<td>This outcome shows the proportion of serious bleeds that stopped or reduced so that the person’s condition became stable within 24 hours of the first susoctocog alfa infusion (injection)&lt;br&gt;In the key study by Kruse-Jarres et al. 2015, bleeding responded to treatment within 24 hours in all 28 people with AHA who received susoctocog alfa&lt;br&gt;This means that a person receiving treatment with susoctocog alfa could expect their bleed to be controlled within 24 hours of the first infusion&lt;br&gt;The study included only 29 participants (1 was later found not to have AHA), was open-label and uncontrolled, and is subject to bias and confounding. Therefore, it is of low-quality and the results should be interpreted with caution. Nevertheless, The European public assessment report for susoctocog alfa states that the design and conduct of the study are acceptable because of the rarity of AHA and the emergency nature of the bleeding, and the marketing authorisation was granted under exceptional circumstances, subject to collection and analysis of further data</td>
</tr>
<tr>
<td>Proportion of serious bleeding episodes successfully controlled at the final</td>
<td>Kruse-Jarres et al. 2015</td>
<td>5/10</td>
<td>Directly applicable</td>
<td>C</td>
<td>24/28 (85.7%)&lt;br&gt;16/17 (94%) treated with susoctocog alfa first-line&lt;br&gt;8/11 (73%) previously treated with a bypassing</td>
<td>This outcome shows the proportion of serious bleeds that, in the opinion of the investigator, were successfully controlled when the person stopped having treatment with susoctocog alfa at the end of the study&lt;br&gt;Kruse-Jarres et al. 2015 found that bleeding was...</td>
</tr>
<tr>
<td>dose</td>
<td>agent</td>
<td>successfully controlled after a course of treatment in more than 8 out of 10 people with AHA who received susoctocog alfa in the study</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>-------</td>
<td>---------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median dose of susoctocog alfa in participants whose primary bleed was successfully controlled</td>
<td>Kruse-Jarres et al. 2015</td>
<td>5/10</td>
<td>Directly applicable</td>
<td>C</td>
<td>In the first 24 hours after treatment initiation: 200.0 units/kg (range 88–400 units/kg) After the first 24 hours: 100.0 units/kg (range 34–400 units/kg)</td>
<td>This outcome shows the average dose of susoctocog alfa that was given in 1 infusion at a single time point, across the 24 people in the study whose bleed was successfully controlled with treatment The average dose in people whose bleed was controlled, was 200 units/kg in the first 24 hours and 100 units/kg after 24 hours The study included only 29 participants, was open-label and uncontrolled, and is subject to bias and confounding. Therefore, it is of low-quality and the results should be interpreted with caution. Nevertheless, The European public assessment report for susoctocog alfa states that the design and conduct of the study are acceptable because of the rarity of AHA and the emergency nature of the bleeding, and the marketing authorisation was granted under exceptional circumstances, subject to collection and analysis of further data</td>
</tr>
<tr>
<td>Parameter</td>
<td>Study Reference</td>
<td>Rating</td>
<td>Applicability</td>
<td>Value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------</td>
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</tr>
<tr>
<td>Median dose of susoctocog alfa</td>
<td>Kruse-Jarres et al. 2015</td>
<td>5/10</td>
<td>Directly applicable</td>
<td>133.0 units/kg (range 34–400 units/kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative dose of susoctocog alfa</td>
<td>Kruse-Jarres et al. 2015</td>
<td>5/10</td>
<td>Directly applicable</td>
<td>1,637.0 units/kg (range 100–20,660 units/kg)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- This outcome shows the average dose of susoctocog alfa that was given in 1 infusion at a single time point, across all 29 people who took part in the study.
- The average dose in everyone who was treated with susoctocog alfa was about 130 units/kg, but varied between different people from below 50 units/kg to 400 units/kg.
- The study included only 29 participants, was open-label and uncontrolled, and is subject to bias and confounding. Therefore, it is of low-quality and the results should be interpreted with caution.
- Nevertheless, The European public assessment report for susoctocog alfa states that the design and conduct of the study are acceptable because of the rarity of AHA and the emergency nature of the bleeding, and the marketing authorisation was granted under exceptional circumstances, subject to collection and analysis of further data.

- This outcome shows the average total dose of susoctocog alfa that was given in a course of infusions throughout the study, across all 29 people who took part in the study.
- The average total dose of susoctocog alfa that people received during the study was about 1,600 units/kg, but varied widely between different people from 100 units/kg to over 20,000 units/kg.
- The study included only 29 participants, was open-label and uncontrolled, and is subject to bias and confounding. Therefore, it is of low-quality and the results should be interpreted with caution.
- Nevertheless, The European public assessment report for susoctocog alfa states that the design and conduct of the study are acceptable because of the rarity of AHA.
| Median number of infusions of susoctocog alfa in all participants exposed to treatment | Kruse-Jarres et al. 2015 | 5/10 | Directly applicable | C | 13.0 Infusions (range 1–140 infusions) | This outcome shows the average number of infusions of susoctocog alfa that were given in each course of treatment throughout the study, across all 29 people who took part in the study. The average number of infusions was 13 in everyone who was treated with susoctocog alfa, but varied widely between different people from 1 to 140. The study included only 29 participants, was open-label and uncontrolled, and is subject to bias and confounding. Therefore, it is of low-quality and the results should be interpreted with caution. Nevertheless, The European public assessment report for susoctocog alfa states that the design and conduct of the study are acceptable because of the rarity of AHA and the emergency nature of the bleeding, and the marketing authorisation was granted under exceptional circumstances, subject to collection and analysis of further data. |
| Median number of days of exposure to susoctocog alfa in all participants exposed to treatment | Kruse-Jarres et al. 2015 | 5/10 | Directly applicable | C | 7.0 days (range 1–25 days) | This outcome shows the average duration of a course of treatment with susoctocog alfa in the study, across all 29 people who took part in the study. Duration of treatment with susoctocog alfa was 7 days, on average, but varied widely between different people from 1 to 25 days. The study included only 29 participants, was open-label and uncontrolled, and is subject to bias and confounding. Therefore, it is of low-quality and the results should be interpreted with caution. |
Nevertheless, The European public assessment report for susoctocog alfa states that the design and conduct of the study are acceptable because of the rarity of AHA and the emergency nature of the bleeding, and the marketing authorisation was granted under exceptional circumstances, subject to collection and analysis of further data.

| Median increase in factor VIII activity levels after the loading dose | Kruse-Jarres et al. 2015 | 5/10 | Directly applicable | C | All participants: 203%  
People with a low antibody titre: 96% (range 73–203%)  
People with a high antibody titre: 29% (range 20–68%) |

This outcome shows how much factor VIII levels increased when susoctocog alfa was given to people in the study. In all people in the study, factor VIII levels, on average, increased by about 200% after the first dose of susoctocog was given. In people with a small amount of antibodies to susoctocog alfa, the average increase in factor VIII seen with treatment was lower, at about 100%. In people with a lot of antibodies to susoctocog alfa, the increase was only about 30%. However, eventually, all participants achieved a rise above 100% after 24 hours, and all had a positive response to treatment after 24 hours.

The study included only 29 participants, was open-label and uncontrolled, and is subject to bias and confounding. Therefore, it is of low-quality and the results should be interpreted with caution. Nevertheless, The European public assessment report for susoctocog alfa states that the design and conduct of the study are acceptable because of the rarity of AHA and the emergency nature of the bleeding, and the marketing authorisation was granted under exceptional circumstances, subject to collection and analysis of further data.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Source</th>
<th>Applicability</th>
<th>Grade</th>
<th>Outcome Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>Kruse-Jarres et al. 2015</td>
<td>Directly applicable</td>
<td>C</td>
<td>This outcome shows the number of people who died during the study</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7 people died during the study. These included 3 deaths due to bleeding, but none of the bleeds were considered related to study treatment or to be due to failure of treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>The study included only 29 participants, was open-label and uncontrolled, and is subject to bias and confounding. Therefore, it is of low-quality and the results should be interpreted with caution. Nevertheless, The European public assessment report for susoctocog alfa states that the design and conduct of the study are acceptable because of the rarity of AHA and the emergency nature of the bleeding, and the marketing authorisation was granted under exceptional circumstances, subject to collection and analysis of further data</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Kruse-Jarres et al. 2015</td>
<td>Directly applicable</td>
<td>C</td>
<td>This outcome shows the number of serious side effects that were thought to be caused by susoctocog in the study</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No serious side effects were reported. Side effects were generally mild or moderate, and most were not considered to be related to treatment with susoctocog alfa</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>The study included only 29 participants, was open-label and uncontrolled, and is subject to bias and confounding. Therefore, it is of low-quality and the results should be interpreted with caution. Nevertheless, The European public assessment report for susoctocog alfa states that the design and conduct of the study are acceptable because of the rarity of AHA and the emergency nature of the bleeding, and the marketing authorisation was granted under exceptional circumstances, subject to collection and analysis of further data</td>
</tr>
</tbody>
</table>
| Anti-pFVIII antibody titres | Kruse-Jarres et al. 2015 | 5/10 | Directly applicable | C | 5/29 people developed anti-pFVIII antibodies during treatment | This outcome shows the number of people who developed antibodies to susoctocog alfa. Antibodies may reduce the treatment’s ability to reduce or stop bleeding.  
5 people developed antibodies to susoctocog alfa. Bleeding was not controlled in 2 of these people.  
The study included only 29 participants, was open-label and uncontrolled, and is subject to bias and confounding. Therefore, it is of low-quality and the results should be interpreted with caution. Nevertheless, The European public assessment report for susoctocog alfa states that the design and conduct of the study are acceptable because of the rarity of AHA and the emergency nature of the bleeding, and the marketing authorisation was granted under exceptional circumstances, subject to collection and analysis of further data. |

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*a* Not all participants were assessed at all time-points  
*b* Overall control of the bleeding episodes was not achieved in 4 people, although they had a positive response to treatment at the 24-hour assessment. These people were later withdrawn from the study because, for example, subsequent bleeds were not successfully controlled or medical complications occurred.

Abbreviations: pFVIII, porcine factor VIII
Relevance to guidelines and NHS England policies

NHS England and NICE have not issued any guidelines or policies on managing acquired haemophilia A with susoctocog alfa.


References

Fosbury E, Drebes A, Riddell A et al. (2017) Review of recombinant anti-haemophilic porcine sequence factor VIII in adults with acquired haemophilia A. Therapeutic Advances in Hematology 8(9): 263–72


Appendix 1 Search strategy

**Database**: Ovid MEDLINE(R) Epub Ahead of Print; In-Process & Other Non-Indexed Citations; Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)

**Platform**: Ovid

**Version**: 1946 - present

**Search date**: 13/09/17

**Number of results retrieved**: 117

**Search strategy**:

1. susoctocog.ti,ab. (4)
2. obizur.ti,ab. (7)
3. obi-1.ti,ab. (13)
4. obi1.ti,ab. (1)
5. BAX801.ti,ab. (2)
6. BAX 802.ti,ab. (0)
7. (PFVIII or "Porcine FVIII" or "Recombinant porcine factor VIII" or RpfVIII).ti,ab. (125)
8. ("Recombinant coagulation factor VIII" and porcine).ti,ab. (3)
9. or/1-8 (138)
10. hemophilia a/ (19712)
11. ("acquired haemophilia" or "acquired hemophilia" or "haemophilia A" or "hemophilia A or factor 8" or "factor VIII").ti,ab. (17998)
12. ("haemophilia type A" or "hemophilia type A").ti,ab. (36)
13. Factor VIII/ (15868)
14. or/10-13 (34109)
15. 9 and 14 (131)
16. limit 15 to english language (126)
17. limit 16 to (letter or historical article or comment or editorial) (9)
18. 16 not 17 (117)

**Database**: Embase

**Platform**: Ovid

**Version**: 1974 to September 12

**Search date**: 13/09/17

**Number of results retrieved**: 104

**Search strategy**:

1. susoctocog.ti,ab. (4)
2. obizur.ti,ab. (11)
3. obi-1.ti,ab. (48)
4. obi1.ti,ab. (1)
5. BAX801.ti,ab. (2)
6. BAX 802.ti,ab. (0)
7. (PFVIII or "Porcine FVIII" or "Recombinant porcine factor VIII").ti,ab. (185)
8. ("Recombinant coagulation factor VIII" and porcine).ti,ab. (3)
9. or/1-8 (214)
10. hemophilia a/ (18828)
11. ("acquired haemophilia" or "acquired hemophilia" or "haemophilia A" or "hemophilia A or factor 8" or "factor VIII").ti,ab. (28960)
12. ("haemophilia type A" or "hemophilia type A").ti,ab. (65)
13. blood clotting factor 8/ (23364)
14. or/10-13 (42537)
15. 9 and 14 (202)
16. limit 15 to english language (198)
17. limit 16 to (letter or editorial) (5)
Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); DARE; CENTRAL; HTA database; NHS EED
Platform: Wiley
Version:
  CDSR – 9 of 12, September 2017
  DARE – 2 of 4, April 2015 (legacy database)
  CENTRAL – 8 of 12, August 2017
  HTA – 4 of 4, October 2016
  NHS EED – 2 of 4, April 2015 (legacy database)
Search date: 13/09/17
Number of results retrieved: CDSR 0 ; DARE 0 ; CENTRAL 6 ; HTA 0 ; NHS EED 0 .
Search strategy:
#1  susoctocog:ti,ab  0
#2  obizur:ti,ab  1
#3  obi-1:ti,ab  1
#4  obi1:ti,ab  0
#5  BAX801:ti,ab  0
#6  BAX 802:ti,ab  0
#7  (PFVIII or "Porcine FVIII" or "Recombinant porcine factor VIII" or RpfVIII):ti,ab  5
#8  ("Recombinant coagulation factor VIII" and porcine):ti,ab  0
#9  {or #1-#8}  6

Clinicaltrials.gov
Search date: 12/09/17
Number of results retrieved: 6
Search strategy:
Searches for obizur, obi-1, susoctocog.

Clinicaltrialsregister.eu
Search date: 12/09/17
Number of results retrieved: 3
Search strategy:
Searches for obizur, obi-1, susoctocog.
Appendix 2 Study selection

The literature search identified 242 records (see appendix 1). When duplicates were removed, this left 125 records, which were screened using their titles and abstracts. The following were excluded:

- abstracts and conference posters
- non-English language studies
- review articles and commentaries
- pharmacokinetic and animal studies
- studies looking at pd-pFVIII and pFVIIa, and
- studies in people with congenital haemophilia A.

Eight full text references were obtained and assessed for relevance. Of these, 4 are included in the evidence summary. The remaining 4 references were excluded and are listed in table 3.

**Table 3 Excluded studies**
<table>
<thead>
<tr>
<th>Study reference</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shatzel JJ, Azar S, Scherber R et al. (2017) Unexpected pharmacokinetics of recombinant porcine factor VIII in a patient with acquired factor VIII deficiency and spontaneous epidural haematoma. Haemophilia Jun 29, epub ahead of print</td>
<td>Single case report concluding that regular monitoring is required, which is already recommended in the product information</td>
</tr>
<tr>
<td>Stemberger M, Möhnle P, Tschöp J et al. (2016) Successful bleeding control with recombinant porcine factor VIII in reduced loading doses in two patients with acquired haemophilia A and failure of bypassing agent therapy. Haemophilia. 22(5): e472–4</td>
<td>Letter describing 4 cases who received a lower loading dose of susoctocog than recommended in the SPC</td>
</tr>
<tr>
<td>Tarantino MD, Cuker A, Hardesty B et al. (2017) Recombinant porcine sequence factor VIII (rpFVIII) for acquired haemophilia A: practical clinical experience of its use in seven patients. Haemophilia 23(1): 25–32</td>
<td>A retrospective chart review describing 7 cases who received a lower loading dose of susoctocog than recommended in the SPC</td>
</tr>
</tbody>
</table>
Figure 1 Flow chart of included studies

Records identified through database searching (n = 242)

Duplicates removed (n = 125)

Records screened (n = 117)

Records excluded at title and abstract sift (n = 109)

Full text articles screened (n = 7)

Records excluded at full text selection (n = 6)

Records included (n = 1)

References to published studies identified by company (n = 3)

Unique references (n = 1)

Records excluded (n = 1)
### Appendix 3 Evidence tables

#### Table 4 Kruse-Jarres et al. 2015

| Unique identifier | NCT01178294 |
| Study type | Prospective, phase II/III multicentre, international, open-label, single-cohort study (P1: primary research using quantitative approaches) |
| Aim of the study | Evaluated the efficacy and safety of susoctocog alfa for treating serious bleeds |
| Study dates | November 2010 to October 2013 |
| Setting | 12 study sites: 8 in the USA, 2 in the UK, 1 in Canada and 1 in India |
| Number of participants | 29 adults (median age 70 years) were enrolled and treated. However, 1 person was later shown not to have factor VIII autoantibodies |
| | 18 people completed the study |
| Population | People aged 18 years or more with AHA and a serious bleed (for example, a bleed threatening vital organ function, requiring a blood transfusion, compromising muscle viability or neurovascular integrity, or impacting a major joint) |
| | Presenting bleeds were in muscle or joints (n=20), intracranial (n=1), retroperitoneal (n=1), peri-orbital (n=1) and post-surgery (n=3). Susoctocog alfa was administered as surgical prophylaxis in 2 people. |
| | 13 people had underlying malignancies, autoimmune disorders or infections. Median factor VIII activity was 3% |
| | 11 participants received haemostatic agents within 1 month of treatment with susoctocog alfa (7 rFVIIa, 3 aPCC and 3 tranexamic acid). All participants received immunosuppressive therapy (corticosteroids alone or with cyclophosphamide or rituximab) |
| Inclusion criteria | A life expectancy of at least 90 days before the bleed |
| Exclusion criteria | Haemodynamic instability (after volume replacement) |
| | A bleeding episode likely to resolve on its own if left untreated |
| | An anti-pFVIII antibody titre exceeding 20 Bethesda units |
| | Use of rFVIIa within 3 hours or aPCC within 6 hours of administration of susoctocog alfa |
| Intervention(s) | All participants received a loading dose of IV susoctocog alfa 200 units/kg bodyweight. Additional doses were at the discretion of the investigator based on factor VIII activity level and clinical assessment of response to treatment |
| | For severe bleeds of ‘particular concern’, the target trough |
factor VIII activity level was at least 80%, otherwise it was over 50%.

**Comparator(s)**
None

**Length of follow-up**
Participants were followed for 90 days (±7 days) after the final dose of susoctocog alfa

**Outcomes**

**Primary outcome:**
- The proportion of serious bleeding episodes that responded to susoctocog alfa 24 hours after initiation of treatment

  The initial ('qualifying' or primary) serious bleeding episode for each subject was analysed using a 4-point scale:
  - effective (bleeding stopped with clinical control and factor VIII levels of 50% or higher)
  - partially effective bleeding reduced with clinical stabilisation and factor VIII levels of 20% or higher
  - poorly effective (bleeding slightly reduced or unchanged and factor VIII levels of less than 50%)
  - not effective (bleeding worsening and factor VIII levels less than 20%)

  A 'positive response' was defined as 'effective' or 'partially effective' control of bleeding, as determined by the investigator using the rating scale

**Selected secondary outcomes:**
- The overall proportion of serious bleeding episodes successfully controlled with susoctocog alfa at the final dose, as assessed by the investigator using a checklist of anticipated sites of bleeding
- The proportion of bleeding episodes that responded to susoctocog alfa at designated assessment time points after the initiation of therapy, as assessed by the investigator
- Frequency, total dose, and total number of infusions of susoctocog alfa required to successfully control primary bleeding episodes
- Factor VIII activity levels
- Efficacy in people with anti-pFVIII antibodies

**Safety outcomes:**
- Treatment-emergent adverse events
- Serious adverse events
- Anti-pFVIII antibody titres

Safety outcomes were assessed by an independent data and safety monitoring board

**Source of funding**
Baxter Healthcare

**Abbreviations**
AHA, acquired haemophilia A; aPCC, activated prothrombin complex concentrate; CHMP, Committee for Medicinal Products for Human Use; IV, intravenous; pFVIII, porcine factor VIII; rFVIIa, activated recombinant factor VII

**Comments**
* The European public assessment report for susoctocog alfa stated that 18 were white, 6 were black or African-American and 5
were Asian

\(^b\) The Bethesda assay is used to quantify the concentration of a factor VIII inhibitor. 1 Bethesda unit is the amount of inhibitor required to neutralise 50% of a unit of factor VIII in normal plasma after incubation at 37°C for 2 hours

\(^c\) Factor VIII was measured using a standard one-stage clotting or chromogenic assay using the World Health Organisation human factor VIII plasma standard

### Modified NSF-LTC

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score</th>
<th>Narrative description of study quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Are the research questions/aims and design clearly stated?</td>
<td>1/2</td>
<td>The research questions are stated and the design is clearly stated. However, the study was open-label and uncontrolled, and subject to bias and confounding. Therefore, it is insufficient to reliably answer the research questions, and the results should be interpreted with caution.</td>
</tr>
<tr>
<td>2. Is the research design appropriate for the aims and objectives of the research?</td>
<td>1/2</td>
<td>The European public assessment report for susoctocog alfa states that the design of the study and use of clinical judgement to assess the primary endpoint are known to be susceptible to bias. However, it also notes that, given the rarity of AHA and the emergency nature of serious bleeding, the design and conduct of the study are acceptable.</td>
</tr>
<tr>
<td>3. Are the methods clearly described? Are the methods appropriate?</td>
<td>1/2</td>
<td>The methods are clearly described. The European public assessment report for susoctocog alfa states that the study follows the various CHMP Scientific advices. However, the weaknesses in the design and conduct of the study are acknowledged.</td>
</tr>
<tr>
<td>4. Are the data adequate to support the authors' interpretations/conclusions? Have issues of bias, confounding and study power been considered and addressed?</td>
<td>1/2</td>
<td>The data are not adequate to support firm conclusions. Nevertheless, the European public assessment report for susoctocog alfa states that the marketing authorisation was</td>
</tr>
</tbody>
</table>
granted under exceptional circumstances based on this study, subject to the company collecting and analysing immediate and long-term data on clinical efficacy and safety in all people with AHA who are treated with susoctocog alfa.

5. Are the results generalisable to the decision problem?  

<table>
<thead>
<tr>
<th></th>
<th>1/2</th>
<th>The results are generalisable to the decision problem. However, the study included only 29 participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>5/10</td>
<td></td>
</tr>
<tr>
<td>Applicability</td>
<td>Directly / indirectly applicable</td>
<td>Direct study focusing on people with the indication and characteristics of interest</td>
</tr>
</tbody>
</table>

### Appendix 4 Results tables

Table 5 Kruse-Jarres et al. 2015
<table>
<thead>
<tr>
<th>Susoctocog alfa</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>28&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

### Primary outcome

The proportion of serious bleeding episodes that responded<sup>b</sup> to susoctocog alfa 24 hours after initiation of treatment

28/28 (100%, 95% CI 88.1% to 100%)

### Selected secondary outcomes

<table>
<thead>
<tr>
<th>Outcome Description</th>
<th>Outcome Details</th>
</tr>
</thead>
</table>
| The proportion of bleeding episodes that responded<sup>b</sup> at designated assessment time points after the initiation of therapy | 19/20<sup>c</sup> (95%) had a positive response at 8 hours  
18/18<sup>c</sup> (100%) had a positive response at 16 hours |
| The proportion of serious bleeding episodes successfully controlled<sup>d</sup> with susoctocog alfa at the final dose | 24/28 (85.7%)<sup>e</sup>  
16/17 (94%) treated with susoctocog alfa first-line  
8/11 (73%) previously treated with a bypassing agent |
| Median cumulative dose of susoctocog alfa in the first 24 hours after treatment initiation in participants whose primary bleed was successfully controlled (n=24) | 458.7 units/kg (range 100–2,100 units/kg) |
| Median dose of susoctocog alfa in the first 24 hours after treatment initiation in participants whose primary bleed was successfully controlled (n=24) | 200.0 units/kg (range 88–400 units/kg) |
| Median number of infusions of susoctocog alfa in the first 24 hours after treatment initiation in participants whose primary bleed was successfully controlled (n=24) | 3.5 infusions (range 1–7 infusions) |
| Median dosing interval for susoctocog alfa in the first 24 hours after treatment initiation in participants whose primary bleed was successfully controlled (n=20<sup>f</sup>) | 7.4 hours (range 3–23 hours) |
| Median dose of susoctocog alfa after the first 24 hours in participants whose primary bleed was successfully controlled (n=21<sup>g</sup>) | 100.0 units/kg (range 34–400 units/kg) |
| Median cumulative dose of susoctocog alfa in all participants exposed to treatment (n=29<sup>h</sup>) | 1,637.0 units/kg (range 100–20,660 units/kg) |
| Median dose of susoctocog alfa in all participants exposed to treatment (n=29<sup>h</sup>) | 133.0 units/kg (range 34–400 units/kg) |
| Median number of infusions of susoctocog alfa in all participants exposed to treatment (n=29<sup>h</sup>) | 13.0 Infusions (range 1–140 infusions) |
| Median number of days of exposure to susoctocog alfa in all participants exposed to treatment (n=29<sup>h</sup>) | 7.0 days (range 1–25 days) |
**Median increase in factor VIII activity levels after the loading dose in all participants exposed to treatment (n=29³)**

<table>
<thead>
<tr>
<th>Activity Level</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>203%</td>
</tr>
</tbody>
</table>

**Median increase in factor VIII activity levels after the loading dose in people with anti-pFVIII antibodies (n=10)**

<table>
<thead>
<tr>
<th>Activity Level</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>96% (range 73–203%) in people with a low antibody titre (n=6)</td>
</tr>
<tr>
<td></td>
<td>29% (range 20–68%) in people with a high antibody titre (n=4)</td>
</tr>
<tr>
<td></td>
<td>With repeated dosing, all 10 participants achieved a rise above 100% after 24 hours. All had a positive response to treatment after 24 hours</td>
</tr>
</tbody>
</table>

**Safety and tolerability outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>7 deaths occurred during the study. These included 3 bleeds, but none were considered related to study treatment or to be due to failure of treatment</td>
</tr>
<tr>
<td>Serious treatment-related adverse events</td>
<td>None</td>
</tr>
<tr>
<td>Anti-pFVIII antibody titres</td>
<td>5 people developed anti-pFVIII antibodies during treatment. Bleeding was not controlled in 2 of these people</td>
</tr>
</tbody>
</table>

³ 10 people discontinued treatment (3 experienced adverse events, 2 developed anti-pFVIII inhibitors, 1 experienced lack of efficacy, 1 was lost to follow-up, 1 became terminally ill, 1 died and 1 was non-compliant

² A ‘positive response’ was defined as ‘effective’ or ‘partially effective’ control of bleeding, as determined by the investigator using a rating scale

⁴ Not all participants were assessed at all time-points

⁵ Assessed by the investigator using a checklist of anticipated sites of bleeding

⁶ Overall control of bleeding episodes was not achieved in 4 people, although they had a positive response to treatment at the 24-hour assessment. These people were later withdrawn from the study because, for example, subsequent bleeds were not successfully controlled or medical complications occurred

⁷ 4 participants received only 1 dose within the first 24 hours after treatment initiation

⁸ 3 participants did not receive any infusions to treat the primary bleed after 24 hours

⁹ Includes 1 person who received susoctocog alfa but was found to have no factor VIII autoantibodies

**Abbreviations:** CI, confidence interval; pFVIII, porcine factor VIII
# Appendix 5 Grading of the evidence base

For each key outcome, studies were grouped and the following criteria were applied to achieve an overall grade of evidence by outcome.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade A</td>
<td>More than 1 study of at least 7/10 quality and at least 1 study directly applicable</td>
</tr>
</tbody>
</table>
| Grade B | 1 study of at least 7/10 which is directly applicable OR  
More than 1 study of at least 7/10 which is indirectly applicable OR  
More than 1 study 4-6/10 and at least 1 is directly applicable OR  
1 study 4-6/10 which is directly applicable and 1 study of at least 7/10 which is indirectly applicable |
| Grade C | 1 study of 4-6/10 and directly applicable OR  
Studies 2-3/10 quality OR  
Studies of indirect applicability and no more than 1 study is 7/10 quality |

Applicability should be classified as:

- Direct studies that focus on people with the indication and characteristics of interest
- Indirect studies based on evidence extrapolated from populations with other conditions and characteristics

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