

Susoctocog Alfa: A Review in Acquired Haemophilia A

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Published online: 21 April 2016
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Abstract Intravenous susoctocog alfa (Obizur®) is a recombinant, B-domain deleted, porcine sequence anti-haemophilic factor VIII (FVIII) product that has recently been approved for the treatment of bleeding episodes in adults with acquired haemophilia A (AHA). Intravenous susoctocog alfa was an effective and generally well tolerated treatment for serious bleeding episodes in adult patients with AHA in a multinational, phase II/III trial ($n = 28$ evaluable). Patients received an initial dose of susoctocog alfa 200 U/kg, with subsequent dosages based on target FVIII trough levels and clinical assessments. All patients had a positive haemostatic response (based on predefined criteria) of the primary bleed 24 h after the first infusion of susoctocog alfa, with the bleed successfully controlled at the time of final dosing in 86 % of patients. The most frequently reported adverse reaction (incidence >5 %) was the development of inhibitory antibodies against susoctocog alfa (porcine FVIII). Overall, 25 % of antibody naive patients developed anti-susoctocog alfa antibodies during the study. No serious treatment-related

adverse events, thrombotic events or allergic reactions were reported during the trial. In conclusion, intravenous susoctocog alfa is a useful addition to the limited treatment options available for the management of acute bleeding episodes in adults with AHA.

Susoctocog alfa: clinical considerations

First-in-class recombinant porcine FVIII, B-domain deleted treatment for AHA

Temporarily replaces the inhibited endogenous FVIII that is required for effective haemostasis

A positive response is achieved in all patients 24 h after the initial dose in a pivotal phase II/III trial

Bleeding is completely controlled in the majority of patients

No reports of thrombotic events, allergic reactions or thrombocytopenia in the pivotal trial

Development of inhibitory antibodies to susoctocog alfa (porcine FVIII) is the most frequently reported adverse reaction

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1 Introduction

Acquired haemophilia A (AHA) is a rare but potentially life-threatening bleeding disorder, caused by the spontaneous development of autoantibodies, known as inhibitors, directed against circulating clotting factors (often factor [F] VIII) [1–3]. Most inhibitor antibodies are IgG1 and

IgG4 autoantibodies which bind to the A2, A3 and C2 domains of the FVIII molecule [4]. Thus, these autoantibodies inactivate FVIII, and as a consequence, patients develop complications associated with abnormal bleeding [1–3]. Unlike congenital haemophilia, AHA typically affects older adults and occurs in both males and females [1, 2]. Moreover, the bleeding pattern differs in patients with AHA and affected individuals bleed into the skin, muscles and soft tissues rather than into the joints [1, 2]. The objectives in treating AHA are to control bleeding during acute episodes and to eradicate the autoimmune antibodies (using immunosuppressive regimens) [2, 3].

Bleeding in patients with AHA is variable, ranging from acute, life-threatening haemorrhages to mild bleeding that requires no treatment [1–3]. When treatment is necessary, FVIII-bypassing agents are the standard of care because of their rapid action and high level of effectiveness [2, 3]. Current guidelines recommend the use of activated prothrombin complex concentrates (aPCC; such as FEIBA, which contains FII, FXI and FX mainly in non-activated, and FVII mainly in the activated form) or recombinant activated FVII (rFVIIa; NovoSeven) as first-line haemostatic therapy [2, 3]. However, there is no standardized and validated assay available to measure the *in vivo* efficacy of these agents or to predict individual patient responses to treatment [2]. Furthermore, bypassing agents are associated with a small risk of thromboembolic events [1, 2].

Porcine FVIII has also been used as a replacement therapy to treat bleeding in patients with AHA due to the low cross-reactivity of anti-human FVIII antibodies towards porcine FVIII [1–3, 5]. Hyate:C, a polyelectrolyte chromatographic fractionated plasma concentrate, was the first commercial porcine FVIII product available; however, it was withdrawn from the market in 2004 due to concerns over viral safety (some batches were contaminated with porcine parvovirus) [5, 6]. Susoctocog alfa (Obizur®), a B-domain deleted recombinant porcine FVIII, is a purified glycoprotein produced in baby hamster kidney (BHK) cells by recombinant DNA technology and has recently been approved in several countries, including the EU, the USA and Canada for the treatment of bleeding episodes in adults with AHA [7–9]. This narrative review focuses on the efficacy and tolerability of susoctocog alfa for the treatment of bleeding episodes in adults with AHA and overviews its pharmacological properties.

2 Pharmacodynamic Properties of Susoctocog Alfa

Susoctocog alfa is an 1448 amino acid porcine recombinant FVIII glycoprotein (heterodimer) in which the B-domain has been replaced with a 24 amino acid linker, which

consists of both the N- and C-terminal ends of the native porcine B domain [5, 7]. Between-species differences in the amino acid sequences of the A2 (differ by 16 %) and C2 (24 %) domains of human and porcine FVIII mean that it remains reasonably free from inactivation by circulating inhibitory antibodies against human FVIII [5].

Susoctocog alfa temporarily replaces the inhibited endogenous FVIII and functions in the coagulation cascade to promote haemostasis [7, 8]. *In vitro*, susoctocog alfa binds to von Willebrand factor with $\approx 1:1$ mole equivalent triggering the clotting cascade resulting in the formation of a blood clot [10]. Susoctocog alfa (at doses equivalent up to 400 U/kg bodyweight) dose-dependently corrected thrombin generation and clot structure when added to plasma samples containing low and mid anti-susoctocog alfa titers (<10 Bethesda units [BU]/mL) that were obtained from patients with congenital haemophilia A (CHA) who had inhibitors to FVIII (data available as an abstract) [11]. Correction of thrombin generation parameters was dependent on the anti-susoctocog alfa inhibitor titer, rather than human FVIII inhibitor levels [11].

Animal models of haemophilia A provide support for the use of susoctocog alfa in the clinical setting (data available as an abstract) [12]. Susoctocog alfa dose-dependently reduced the cuticle bleeding time in haemophilic dogs. The estimated susoctocog alfa dose producing 50 % survival after 24 h was 89 U/kg following a standardized tail-snip haemorrhagic insult in FVIII knockout mice [12].

In a phase II study in patients with CHA with inhibitors to human FVIII (unapproved indication), intravenous susoctocog alfa was effective in controlling all 25 bleeding episodes in 9 patients (data available as an abstract) [13, 14]. Dosing was initiated with a loading dose (determined by inhibitor titer, body weight, and haematocrit) followed by up to eight doses of susoctocog alfa 50 U/kg (for the first three doses), 100 U/kg (for the next three doses) or 150 (for the last two doses) based on clinical assessments. The majority of bleeds (20 out of 25) were controlled following one dose of susoctocog alfa (with or without a loading dose). The median total dose of susoctocog alfa was 224.1 U/kg across all bleeding episodes and was 200.8 U/kg for the 20 bleeds controlled with one dose (with or without a loading dose). As a result of these findings, a fixed initial dose of susoctocog alfa 200 U/kg was selected for further studies [13, 14].

In patients with AHA (Sect. 4), susoctocog alfa treatment was associated with considerable variability in peak FVIII activity levels over the first 24 h, which may partly be due to the cross-reactivity of the individual patient's FVIII antibodies with porcine FVIII [15]. For example, FVIII activity increased by 20–540 % (median 203 %) directly after the first dose (200 U/kg). After subsequent dosages, the highest FVIII activity ranged from 160 to

775 % (median 255 %) during the first 24 h period and the median FVIII activity at the time of the primary endpoint measurement (at 24 h) was 108 % [15].

There is a potential for immunogenicity with susoctocog alfa treatment [6, 16]. Inhibitory antibodies against porcine FVIII were detected in haemophilia A mice (pre-sensitized to recombinant human FVIII) [6] and cynomolgus monkeys receiving susoctocog alfa (data available as an abstract) [16]. There were no differences in the formation of total or inhibitory anti-porcine FVIII antibodies between monkeys receiving susoctocog alfa and those receiving Hyate:C [16].

In the phase II/III trial in patients with AHA (Sect. 4), the presence of activity-neutralizing antibodies against susoctocog alfa at baseline had a blunting effect on the immediate increase in FVIII activity following the first susoctocog alfa dose (200 U/kg), but not subsequent FVIII activity levels [15]. After this initial dose, the median increase in FVIII activity levels was 96 and 29 % in patients with low (0.8–4 BU) and high (10–29 BU) susoctocog alfa inhibitor titres, respectively, compared with 257 % in patients with no detectable inhibitors. However, FVIII activity levels were >100 % in all patients following subsequent administration of susoctocog alfa using a tailored dosing regimen, irrespective of baseline anti-susoctocog alfa inhibitor titre [15]. The development of de novo inhibitory antibodies against susoctocog alfa in patients with AHA is discussed in Sect. 5.

3 Pharmacokinetic Properties of Susoctocog Alfa

Pharmacokinetic parameters for susoctocog alfa varied among individuals and differed according to which assay was used to measure FVIII activity (chromogenic assay vs. one-stage clotting assay) [8, 10, 17]. In patients with CHA with anti-human FVIII inhibitors in the non-bleeding state, single dose administration of susoctocog alfa 100 U/kg resulted in a maximum FVIII concentration ($C_{\max}$) [recovery] which varied between 88 and 264 U/dL using one-stage coagulation assay and between 119 and 182 U/dL using the chromogenic assay [17].

Although FVIII activity ascertained by the chromogenic assay is generally lower than that determined by the one-stage clotting assay (Sect. 6), the maximum post-infusion FVIII activity in five patients with AHA in the non-bleeding state was 108 % ($A_{\max}$) when measured by the chromogenic assay compared with 81 % ($C_{\max}$) when evaluated by the one-stage clotting assay (baseline-corrected values) [8, 10]. Unless stated otherwise, the pharmacokinetic parameters discussed hereafter were measured using the one-stage clotting assay.

In five patients with AHA in the non-bleeding state, the time to the peak observed percentage activity ($T_{\max}$) of

susoctocog alfa, without correction for baseline FVIII activity, was ≈ 0.5 h after administration of the final dose (2934–10,000 U) [8, 10]. Following the initial dose of susoctocog alfa (200 U/kg), the mean recovery rate was 1.06 U/ml per U/kg (range 0.10–2.61 U/mL per U/kg) [8]. The mean volume of distribution (baseline-corrected value) was 65.1 U/% activity [10].

Exposure to susoctocog alfa was approximately twofold higher than that of Hyate:C at the same dose (100 U/kg; $n = 3$ in both groups) in patients with CHA with anti-human FVIII inhibitors [17]. This suggests that susoctocog alfa may have a higher bioavailability than Hyate:C, which is possibly due to the purity of susoctocog alfa [17].

No studies have evaluated the metabolism and excretion of susoctocog alfa [10]. The mean terminal half-life of susoctocog alfa was 6.6 h (range 1.8–17 h) in five patients with AHA in the non-bleeding state and was ≈ 10 h (range 2.6–28.6 h) in nine patients with AHA in the bleeding state [8, 10]. Mean plasma clearance was 18.07 U/% activity-time in six patients in the non-bleeding state (baseline-corrected value) [10].

No formal studies have been conducted to evaluate the potential for drug–drug interactions of susoctocog alfa [10]. However, given that it is a recombinant protein, susoctocog alfa is expected to be an unlikely candidate for drug–drug interactions.

4 Therapeutic Efficacy of Susoctocog Alfa

The efficacy of intravenous susoctocog alfa for the treatment of serious bleeding episodes in patients with AHA was evaluated in an open-label, multinational, phase II/III trial ($n = 29$ enrolled) [15]. Patients aged ≥ 18 years (mean age 70 years) experiencing serious bleeding requiring hospitalization (e.g. threatening vital organ function, requiring a blood transfusion, compromising muscle viability or neurovascular integrity or impacting a major joint) with a clinical diagnosis of AHA with autoimmune inhibitory antibodies to human FVIII were eligible for inclusion ($n = 28$ evaluable) [10, 15]. Key exclusion criteria included an anti-susoctocog alfa inhibitor titre of >20 BU and a platelet count of <100,000/ μ L [15].

At screening, the median FVIII activity level was 3 % (range 0–30 %) [15]. In patients with confirmed AHA and autoantibodies to FVIII ($n = 28$), the median FVIII autoantibody titre was 31 BU (range 4–651 BU) [15]. Ten of these patients (36 %) had a detectable (≥ 0.6 BU) anti-susoctocog alfa inhibitor titres (0.8–29 BU [median 4 BU]) and the mean cross-reactivity of the inhibitory antibody to porcine FVIII versus human FVIII was 8.7 % [15]. The majority of the primary (qualifying) bleeds involved bleeding into muscles or joints [10, 15]. Haemostatic

agents [e.g. rFVIIa, aPCC, tranexamic acid] were used in 11 patients within one month of susoctocog alfa administration [15].

Patients initially received a single intravenous infusion of susoctocog alfa 200 U/kg [10, 15]. Subsequent dosages of susoctocog alfa during the first 24 h (up to 400 U/kg every 2 h) were determined by the investigator based on the patient's post-infusion FVIII activity levels (titrated to a target through level of >80 % for a bleeding episode of particular concern [e.g. severe mucosal, intracranial, retro- or intra-abdominal, genitourinary, neck, traumatic, post-operative] and >50 % for all other bleeds [soft tissue, joint, muscle]) and clinical assessments [10, 15]. After the first 24 h, the susoctocog alfa dosage was titrated to target post-infusion trough FVIII levels of ≥ 50 % for all bleeds [15]. All patients received immunosuppressive therapy (i.e. corticosteroids alone or with cyclophosphamide or rituximab) during the study [15].

The primary endpoint was the proportion of patients with a positive haemostatic response to the primary bleed 24 h after the initiation of susoctocog alfa treatment, based on predefined criteria [15]. A positive haemostatic response was defined as effective (bleeding stopped; clinical control; FVIII activity levels ≥ 50 %) or partially effective (bleeding reduced; clinical stabilization or improvement, or alternative reason for bleeding; FVIII activity ≥ 20 %) control of bleeding [15].

Susoctocog alfa was effective for the treatment of serious bleeding episodes in patients with AHA, with all patients judged to have achieved a positive haemostatic response to treatment of the primary bleed 24 h after the first dose (100; 95 % CI 88.1–100) [15]. This positive haemostatic response rate was considered clinically beneficial, since the lower bound of the two-sided 95 % confidence interval exceeded 50 [5, 15]. Of the positive haemostatic responses for the primary bleed at this time-point, 85.7 % were rated as effective responses and 14.3 % as partially effective responses, according to predefined criteria [15]. Most patients had a rapid response to susoctocog alfa treatment, with a positive response seen in 19 of 20 evaluable patients at 8 h and all 18 patients evaluated at 16 h [15]. In a post-hoc subgroup analysis of five surgical patients with AHA, susoctocog alfa was effective for peri- and post-operative management of bleeds, with all patients achieving a haemostatic response to treatment of the primary bleed at 24 h post-infusion (data available as an abstract) [18].

The majority (85.7 %) of patients achieved treatment success, defined as control of the primary bleed at the time of the final treatment dosing [15]. Bleeding was successfully controlled at the time of last dose in 94 % of patients who received susoctocog alfa as 'first-line' treatment (i.e. no haemostatic agents used immediately before the first

susoctocog alfa treatment; $n = 17$) and in 73 % of patients who were treated with other haemostatic agents before susoctocog alfa ($n = 11$). Treatment success for the primary bleed could not be assessed in four patients who prematurely withdrew from the study after the 24-h assessment. Of these patients, two had an effective treatment response and two had a partially effective treatment response at 24 h [15].

In patients who developed *de novo* anti-susoctocog alfa (porcine FVIII) inhibitory antibodies ($n = 5$; Sect. 5), bleeding was not successfully controlled in two patients [15]. One patient died of cholangitis after a fourth bleed had been controlled and one patient experienced a fatal re-bleed at the primary bleeding site 10 days after stopping susoctocog alfa [15].

In patients whose bleeding was ultimately controlled ($n = 24$), the total dose (median 1580 U/kg; range 100–12,194 U/kg), the total number of infusions of susoctocog alfa (median 12.5 infusions; range 1–57) and days of exposure (median 6.5 days; range 1–23) was highly variable [15]. The median dose per patient ranged from 34–400 U/kg (median 116.5 U/kg) [15]. Over the initial 24-h period ($n = 24$), the median susoctocog alfa dose per patient was 200.0 U/kg (88–100 U/kg), the median dosing interval was 7.4 h (range 3–23 h), the median number of infusions was 3.5 (1–7 infusions) and the median cumulative exposure to susoctocog alfa was 458.7 U/kg (100–2100 U/kg) [15]. Four patients only received one dose of susoctocog alfa during the first 24 h. For the period after the first 24 h of treatment until the bleed was controlled ($n = 21$), a median of 11 infusions (median dose of 100 U/kg) were given for a median of 6 days (median total exposure 1050 U/kg) [15].

The ability to measure and monitor FVIII activity levels allowed for significantly lower doses of susoctocog alfa to be utilized during the study to control the bleed [15]. There was a significant reduction (41.2 %; $p < 0.01$) in the median dose for the initial dose compared with the median dose during the first 24-h treatment period ($n = 26$). There was also a significant reduction (by 65.4 %; $p < 0.0001$; $n = 24$) in median dose for the initial 24-h period versus subsequent 24-h periods [15].

5 Tolerability of Susoctocog Alfa

Susoctocog alfa was generally well tolerated in patients with AHA with autoimmune inhibitory antibodies to human FVIII in the pivotal clinical trial [10, 15]. In the safety population ($n = 29$), the total exposure to susoctocog alfa ranged from 100 to 20,660 U/kg (median 1637 U/kg) [15]. Overall, treatment-emergent adverse events occurred in 93 % of patients, with the majority of these

events being of mild (50 %) or moderate (38 %) severity [10]. Three patients (10 %) discontinued treatment with susoctocog alfa due to adverse events (two patients due to the development of inhibitory antibodies to susoctocog alfa) [10]. Serious treatment-emergent adverse events were reported in 13 out of 29 patients (44.8 %) [10].

The most commonly reported mild adverse events were constipation (2.7 % of patients), diarrhoea (2.3 %), peripheral oedema (2.3 %), insomnia (1.9 %) and nausea (1.5 %) and the most commonly reported moderate adverse events included hypokalaemia (3.0 %), pyrexia (1.5 %), constipation, pneumonia, muscle haemorrhage and hypertension (each 1.1 %). Overall, treatment-emergent adverse events were described as severe in six patients (21 %) and included constipation, hypocalcaemia, abdominal pain and joint swelling (each 0.8 %). The most frequently reported serious treatment-emergent adverse events were pneumonia [3 out of 29 patients (10.3 %)] and sepsis [2 out of 29 patients (6.9 %)] [10].

Treatment-related adverse events, as assessed by the investigator, were reported in six patients (20.7 %) [10]. All events were non-serious, mild or moderate in severity and completely resolved [except for one case of positive inhibitory antibodies to susoctocog alfa which was ongoing at the study completion]. Treatment-related adverse events included mild hypotension and constipation in one patient, two occurrences of central catheter line occlusion in one patient, mild hypofibrinogenaemia in one patient, mental status change in one patient and the development of inhibitory antibodies to susoctocog alfa in two patients [10].

Seven deaths occurred during the trial, which included three deaths following haemorrhages (one intestinal and two intracranial), three cases of sepsis and one case of renal failure [10, 15]. While three of the seven deaths were as a result of bleeding, no death was considered drug-related and no bleeding case was deemed to be caused by lack of efficacy. At the time of death, two of the three patients had received haemostatic treatment other than susoctocog alfa. One patient, with a history of hypertension was given rFVIIa to stop an intracranial haemorrhage and another patient, who stopped susoctocog alfa treatment because of the development of anti-drug antibodies, received aPCC for a re-bleed at the primary site [10, 15].

High and sustained FVIII activity in blood results in a hypercoagulable state which may increase the risk of thromboembolic events, particularly in patients with pre-existing cardiovascular disease [19]. No confirmed cases of thromboembolic events were reported in the pivotal phase II/III trial [15].

Due to the manufacturing process, traces of hamster proteins may cause hypersensitivity or allergic reactions [7, 8, 10]. There were no reports of hypersensitivity reactions following the administration of susoctocog alfa during the

trial [15]. Nevertheless, patients should be monitored for the early signs of hypersensitivity reactions (e.g. hives, generalized urticaria, tightness of the chest) during the susoctocog alfa infusion and susoctocog alfa should be immediately discontinued if allergic or anaphylactic-type reactions do occur [7, 8]. No patients developed an anti-host cell protein BHK antibody titre after exposure to susoctocog alfa (one patient had a positive titre before treatment) [7, 8].

As susoctocog alfa is a therapeutic protein, there is potential for an immune response against the agent (Sect. 2). At baseline, 19 out of 29 patients were negative (i.e. a titre <0.6 BU/ml using a Bethesda assay) for neutralizing anti-susoctocog alfa antibodies [7, 15]. Following treatment with susoctocog alfa, five patients (25 %) developed de novo anti-susoctocog alfa antibodies between 8 to 85 days after the first infusion [7, 15]. Two of these five patients were assessed as having a treatment-related non-serious adverse event and treatment was discontinued [10, 15]. Of the ten patients with detectable anti-susoctocog alfa antibodies at baseline, two patients (20 %) had an increase in titre and eight patients (80 %) had a decrease in titre to a non-detectable level [7].

6 Dosage and Administration of Susoctocog Alfa

Susoctocog alfa is approved for the treatment of bleeding episodes in patients with acquired haemophilia caused by antibodies to FVIII in the USA [7], the EU [8] and Canada [9]. The recommended initial dose of susoctocog alfa is 200 U/kg, given as an intravenous injection at a rate of 1–2 mL/min [7, 8]. Subsequently, the susoctocog alfa dose, frequency (every 4–12 h) and duration of treatment should be based on the location and severity of bleeding episode, results of trough FVIII activity [to be maintained within recommended limits (>50% for minor and moderate bleeding and >80 % [8] or ≥ 100 % [7] for major bleeding) to a maximum of 200 % of normal or 200 U/dL] and on the clinical response achieved [7, 8]. During the healing phase (once bleeding has responded), susoctocog alfa should be continued to maintain trough FVIII activity at 30–40 % (to a maximum of 200 %) until bleeding is controlled with the length of treatment dependent on clinical judgment [8].

FVIII activity should be measured 30 min and 3 h after the initial dose and then immediately before and 30 min after subsequent doses [7, 8]. Of note, FVIII activity established by the chromogenic assay is generally lower than FVIII activity ascertained by the one-stage clotting assay (20–50 %) [7]. Measurements of the FVIII activity must always be carried out using the same assay methodology on any one patient [7, 8]. The one-stage assay is recommended as it was used to determine the mean recovery rate and potency of susoctocog alfa (Sect. 2) [7, 8].

Local prescribing information should be consulted for further information relating to susoctocog alfa, including special warnings and precautions, use in special populations and contraindications.

7 Current Status of Susoctocog Alfa in Acquired Haemophilia A

Intravenous susoctocog alfa is the first recombinant porcine sequence FVIII product to be approved for the treatment of bleeding episodes in adults with AHA in the EU, the USA and Canada [7, 8]. The amino acid sequence of susoctocog alfa exhibits a high-level of similarity to that of human FVIII (Sect. 2) and thereby provides effective haemostasis, while being sufficiently different to render it less susceptible to inactivation by the autoantibodies to FVIII [1, 3, 5, 6]. Like human FVIII, susoctocog alfa acts as a cofactor of the tenase complex, resulting eventually in the development of a fibrin clot and thus promoting coagulation (Sect. 2). Unlike porcine plasma-derived Hyate:C, which was withdrawn from the market due to a risk of transmission of infectious agents, susoctocog alfa is produced using genetically engineered BHK cells, with the protein purified using a sequence of chromatography and filtration steps [5, 7]. The manufacturing process also incorporates two dedicated viral clearance steps (solvent/detergent treatment step and nanofiltration through a series of two 15-nm filters) to reduce the potential for viral contaminants [5, 7, 8]. Moreover, the use of susoctocog alfa is not associated with the occurrence of thrombocytopenia and allergic reactions which were frequent with Hyate:C due to its plasmatic origin [5, 6].

In the pivotal phase II/III trial, all 28 evaluable patients had a positive haemostatic response to treatment (bleeding stopped or reduced) of the primary bleed 24 h after the initiation of susoctocog alfa, with the primary bleed successfully treated in 86 % of patients at the time of final dosing (Sect. 4). Susoctocog alfa was fast-acting, with 95 and 100 % of evaluable patients responding 8 and 16 h after the first dose (Sect. 4). The ability to measure FVIII levels by a standard assay during treatment allowed for the ability to individually tailor the susoctocog alfa dosage following the initial 200 mg dose, which resulted in significantly lower doses used over subsequent treatment periods (Sect. 4).

The trial design (open-label, single-cohort, non-randomized), use of clinical judgment (as opposed to exclusive objective measurements) as a part of the assessment of the primary endpoint (FVIII measurements were objective) and small patient number are limitations of the pivotal study; however, due to the rarity of the population and the fact that patients with AHA, who present with life- or limb-

threatening bleeding are seriously ill, these limitations are considered acceptable [10].

Susoctocog alfa was generally well tolerated in patients with AHA (Sect. 5). The most frequently reported adverse event (incidence ≥ 5 %) was the development of inhibitory antibodies to susoctocog alfa. Although inhibitory antibodies to susoctocog alfa may have the potential to reduce the efficacy of susoctocog alfa, no correlation was found between baseline anti-susoctocog alfa inhibitor titres and the final efficacy outcomes in patients with AHA (Sects. 2 and 4) [7, 8]. The immunogenicity of susoctocog alfa is dependent on the sensitivity and specificity of the different assays used to detect anti-susoctocog alfa antibodies, with assay methodology, sample handling, the timing of sample collection, concomitant medications, and underlying disease having an effect on antibody positivity. Comparisons of antibody rates with those from other products are limited because immunogenicity analyses are product specific [6]. There were no reports of hypersensitivity reactions or thromboembolic events during the study.

A post-marketing safety surveillance study (NCT02610127) is being conducted to further assess safety, utilization and effectiveness of susoctocog alfa in patients with AHA in the real-world setting. In the meantime, intravenous susoctocog alfa, given at an initial dosage of 200 U/kg with subsequent administration based on clinical response and FVIII levels, is an effective and generally well-tolerated treatment for severe bleeding episodes in adults with AHA. Unlike bypassing therapies, treatment with susoctocog alfa allows for FVIII activity monitoring, thereby, guiding dosing and reducing the possibility of under or overdosing. Moreover, susoctocog alfa is highly purified; therefore, the potential to transmit animal or human viruses are low. Thus, intravenous susoctocog alfa is a useful addition to the limited treatment options available for the management of acute bleeding episodes in adults with AHA.

Data selection sources: Relevant medical literature (including published and unpublished data) on susoctocog alfa was identified by searching databases including MEDLINE (from 1946), PubMed (from 1946) and EMBASE (from 1996) [searches last updated 11 April 2016], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug

Search terms: Susoctocog, Obizur, BAX-801, OBI-1, haemophilia A, hemophilia A, factor VIII, FVIII

Study selection: Studies in adult patients with acquired haemophilia A who received susoctocog alfa. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Acknowledgments During the peer review process, the manufacturer of susoctocog alfa was also offered an opportunity to review this article. Changes resulting from comments received were made on the basis of scientific and editorial merit.

Compliance with Ethical Standards

Funding The preparation of this review was not supported by any external funding.

Conflict of interest Celeste B. Burness and Lesley J. Scott are salaried employees of Adis/Springer, are responsible for the article content and declare no relevant conflicts of interest.

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