Clinical Commissioning Policy: Susoctocog alfa for treating bleeding episodes in people with acquired haemophilia A (all ages)

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Clinical Commissioning Policy: Susoctocog alfa for treating bleeding episodes in people with acquired haemophilia A (all ages)

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Policy Statement

NHS England will commission susoctocog alfa for treating bleeding episodes in patients with acquired haemophilia A in accordance with the criteria outlined in this document.

In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

This policy document outlines the arrangements for funding of this treatment for the population in England.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to suspend or rescind policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and

- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Plain Language Summary

See also, section 4 for additional definitions of terms used in this document.

About acquired haemophilia A

Acquired haemophilia A (AHA) is a rare disorder caused by antibodies to factor VIII (a protein needed for blood clotting). The lack of functional factor VIII in the blood, which the antibodies cause, results in a high risk of spontaneous bleeding, or of bleeding in response to minimal trauma or as a result of surgery.

About current treatments

The aims of treating people with AHA are, firstly, to stop a current bleed and, secondly, to stop the production of anti-factor VIII antibodies. When bleeding occurs in people with AHA, giving concentrated human factor VIII does not stop the bleeding, because it is rapidly removed by the factor VIII antibodies. Therefore, a different type of clotting factor that does not rely on the action of 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 antibody. They include activated prothrombin complex concentrate (aPCC, which contains various clotting factors) and activated recombinant factor VII (rFVIIa). Bypassing agents can increase the risk of thrombosis (blood clots forming inside blood vessels) which can be serious.

About the new treatment

Susoctocog alfa is a purified, recombinant (synthetic) porcine factor VIII that is produced by genetic technologies from the factor VIII gene in pigs. It is different enough from human factor VIII to either go undetected or only be partially detected

by the antibody to the human factor VIII (also known as cross-reaction). However, the protein is still similar enough to allow clotting to occur, which stops the bleeding.

What we have decided

NHS England has carefully reviewed the evidence to treat acquired haemophilia A with susoctocog alfa. We have concluded that there is enough evidence to consider making the treatment available.

1 Introduction

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 elimination from the blood of 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 (where pressure within one of the body's compartments results in insufficient blood supply to tissue), haematuria (blood in urine), gastrointestinal bleeding and prolonged bleeding after giving birth. Bleeding may be life or limb-threatening; the reported mortality rate for AHA is between 3% and 22%. Therefore, people with AHA who present with bleeding are in need of urgent, specialist attention.

Susoctocog alfa is a purified, recombinant porcine factor VIII that is made using the factor VIII gene isolated from the pig genome. The purified protein temporarily replaces the human factor VIII as it is different enough to either go undetected or only be partially detected by the antibody to the human factor VIII (also known as cross-reaction). However, the protein is still similar enough to allow coagulation to occur, which stops the bleeding. In contrast to current bypassing agents, susoctocog alfa is measurable in a routine haemostasis laboratory, enabling more accurate and guided dosing.

Susoctocog alfa is expressed in a genetically engineered hamster kidney cell line which secretes recombinant porcine FVIII into the cell culture medium. The recombinant protein is purified using a series of steps and no additives of human or animal origin are used in the formulation of susoctocog alfa. This information should be shared with the patient or carer to ensure they are satisfied that the product is compatible with their religious, cultural or other beliefs or behaviours. To date the manufacturer has not received any issues globally regarding religious objections to

the use of susoctocog alfa.Susoctocog alfa is indicated for the treatment of bleeding episodes in patients with AHA caused by antibodies to factor VIII.

2 Definitions

- **Antibody titre** - Amount of antibody in the bloodstream.
- **aPCC** - Activated prothrombin complex concentrate, a treatment for bleeding in people with certain clotting factor deficiencies. It contains clotting proteins known as factors and includes factor II (two), VII (seven), IX (nine) and X (ten).
- **Arthropathy** - A disease of the joints.
- **Bethesda Units (BU)** - The Bethesda assay is used to quantify the concentration of factor VIII inhibitor. One 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.
- **Central venous access device (CVAD)** – a tube that is inserted into and positioned within a vein in the body to allow treatments to be delivered into the bloodstream.
- **Porcine** – from pigs.
- **Recombinant activated factor VII (rFVIIa)** - an activated form of factor VII which bypasses factors VIII and IX and stops bleeding without the need for factor VIII.
- **Inhibitors** - antibodies developed by the body's immune system stopping certain specific clotting proteins from working properly.

3 Aims and Objectives

This policy considered: Susoctocog alfa for treating bleeding episodes in people with acquired haemophilia A (all ages).

The objectives were to:

- ensure evidence based commissioning with the aim of improving outcomes for patients with acquired haemophilia A; and
- Identify clinical criteria for treating patients with acquired haemophilia A.

4 Epidemiology and Needs Assessment

AHA has an incidence of about 1.5 people in 1,000,000 people per 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 historical AHA were on the register between those dates, 102 of whom were treated (21.4%).

People with AHA who have a bleeding episode are currently treated using a by-passing agent such as activated prothrombin complex concentrate or recombinant FVIIa. Both agents can achieve haemostasis by generating thrombin (without requiring FVIII) at the site of bleeding. However, these should only be used under close supervision of a consultant haematologist with AHA experience due to the increased risk of thrombotic events. The risk of thrombotic events may already be raised in these patients, who tend to be older and can have other conditions that can increase thrombotic risk (including cardiovascular disease or cancer). Neither bypassing agent is measurable in routine, service laboratories. Consequently, dosing is based on the physical effect of treatment which is judged by clinical outcomes such as when an active bleed is stopped.

The ultimate goal is to eliminate the inhibitor that is causing the AHA through immune suppression, including steroids with or without chemotherapy or immunotherapy agents (for example, cyclophosphamide or rituximab). This treatment does not stop a person from bleeding while inhibitors are still present (as the antibodies inactivate and remove the FVIII from the blood).

Management of AHA includes treatment of a bleeding episode and eradication of inhibitor as without the latter the disease is mostly fatal. Treatment with susoctocog alfa could bridge the gap for someone with AHA who has an active bleed while the effect of immune suppression takes effect. Susoctocog alfa could help stop the

bleeding, especially in people at risk of thrombosis or who need close monitoring of the factor levels until such time as the bleed is resolved and the inhibitor eradicated (Fosbury, 2017).

5 Evidence Base

NHS England has concluded that there is sufficient evidence to support the routine commissioning of this treatment for the indication.

The main evidence for the efficacy and safety of susoctocog alfa came from one study that was included in the clinical evidence review.

Kruse-Jarres et al. 2015 was an uncontrolled prospective open-label study in 29 people with AHA (median age 70 years) with a serious bleed (one that threatened vital organ function or required a blood transfusion).

Proportion of serious bleeding episodes that responded to susoctocog alfa treatment

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 which 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 alfa 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 alfa (anti-pFVIII specific 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.

Anti-human Factor VIII antibody that cross-reacts with susoctocog alfa

Ten people in the study had anti-FVIII antibodies which also reacted against susoctocog alfa. Of these, the median increase in factor VIII activity after the loading dose of susoctocog alfa was 96% (range 73–203%) in 6 people 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.

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, often presenting out of hours as medical emergencies. 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.

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-susoctocog alfa antibodies during treatment, anticipated as inevitable based on prior experience with a plasma-derived porcine FVIII (HyateC). 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-susoctocog alfa antibodies, these were subsequently considered unrelated to treatment.

6 Criteria for Commissioning

Criteria for starting treatment:

Susoctocog alfa should be used within its recommended licensed dose as an alternative first-line clotting agent to treat bleeding in people with a confirmed diagnosis of AHA:

- who have an active bleed; and
- who are at a treatment centre which specialises in the treatment of acquired haemophilia A; and
- for whom, in the opinion of a clinician experienced in assessing and treating AHA (as defined in the governance arrangements and patient pathway), susoctocog alfa is considered clinically appropriate.

- the starting dose should be based on clinical need and presentation by an experienced clinician in the range 100 to 200 units per kg bodyweight.
- treatment should be reassessed at 24 hours. On-going treatment after the first 48 hours should be agreed by an appropriate MDT.
- subsequent doses should be guided by regular FVIII assay to a maximum dose of 200 units per kg bodyweight per dose.

Continuation Criteria:

Susoctocog alfa treatment should be reassessed by a local haemophilia MDT if:

- there is evidence of the development of inhibitors specific to susoctocog alfa.

Stopping Criteria:

Treatment with susoctocog alfa must not exceed 25 consecutive days apart from in exceptional circumstances where a UK-wide Haemophilia Centre Doctors' Organisation MDT review considers it clinically appropriate to continue treatment because the patient's bleeding has not responded to bypassing agents or is a serious bleed.

Susoctocog alfa treatment should be discontinued if:

i. there is evidence that susoctocog alfa is no longer working by clinical judgement with failure to control bleeding after 24-48 hours and adequate susoctocog alfa dosing has been confirmed by assay; or
ii. any patient fails to achieve a porcine factor VIII activity level of at least 50 IU/dL (lower end of normal range)
    a. after at least two doses; or
    b. after receiving more than 800 units/kg in a 24 hour period unless included in a care plan approved by a UK HCSO MDT; or
iii. cross-reacting antibodies (anti-pFVIII titre >5 to 6 BU/mL) to susoctocog alfa are detected.

Some people with AHA have antibodies against human FVIII which also cross-react with susoctocog alfa, meaning the antibodies may bind to susoctocog alfa (anti-pFVIII antibodies). This can impair the effectiveness of susoctocog alfa. Treatment with susoctocog alfa will depend on the level of antibodies present. If a person has a

high level (known as titre) of anti-pFVIII antibody (more than 5.0 to 6.0 BU/ml), then susoctocog alfa should not be used except in patients not responding to rFVIIa and aPCC, or who have intracranial bleeds or are undergoing major surgery.

Some people who have been treated with susoctocog alfa previously can form antibodies which are specific to it and inactivate it partially or entirely. If someone has been treated with susoctocog alfa previously, and antibodies to susoctocog alfa are present, the patient should be reassessed before treatment continuation. If the bleed does not respond to treatment with susoctocog alfa, treatment should be stopped.

7 Patient Pathway

Figure 1 Pathway for patients at a non-specialist centre

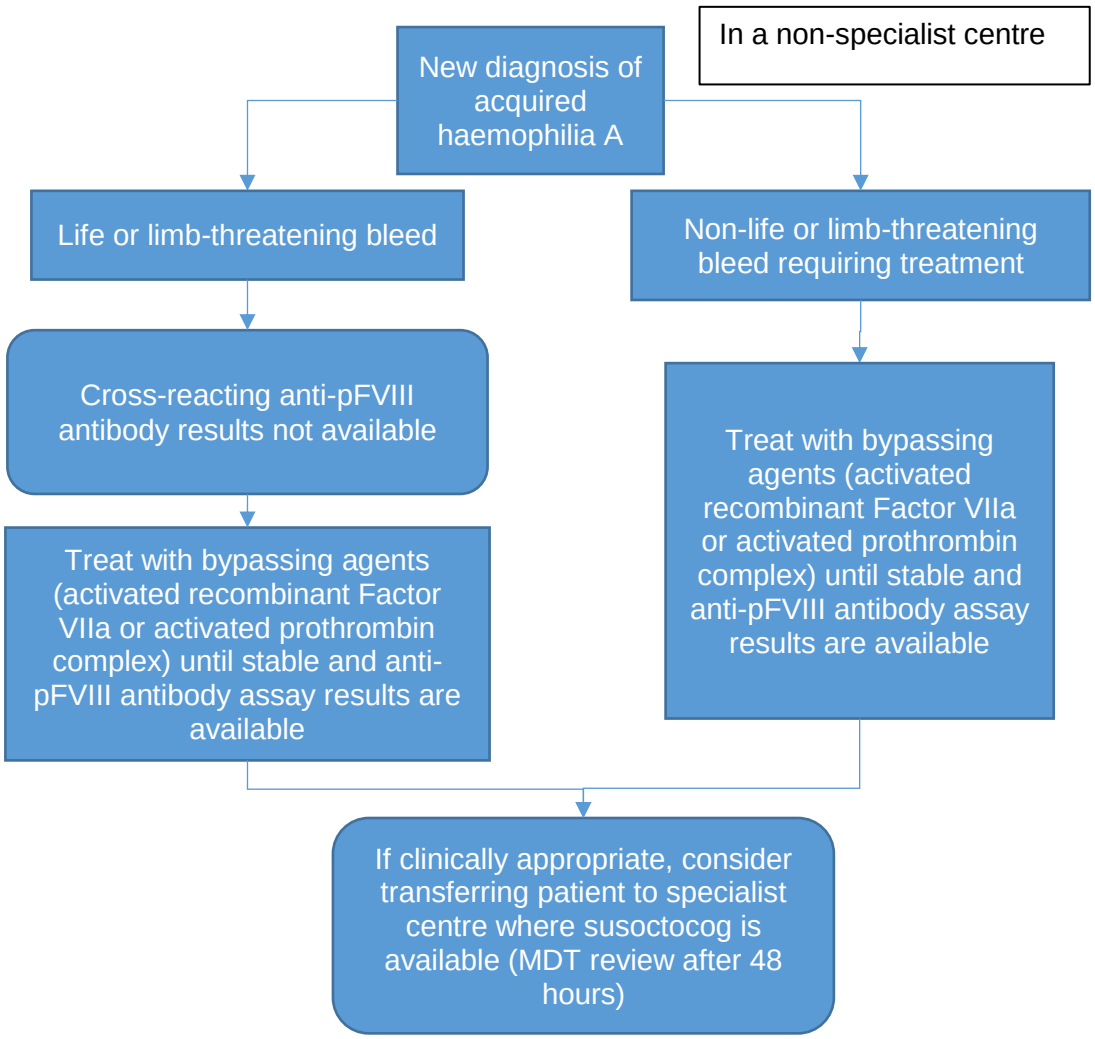
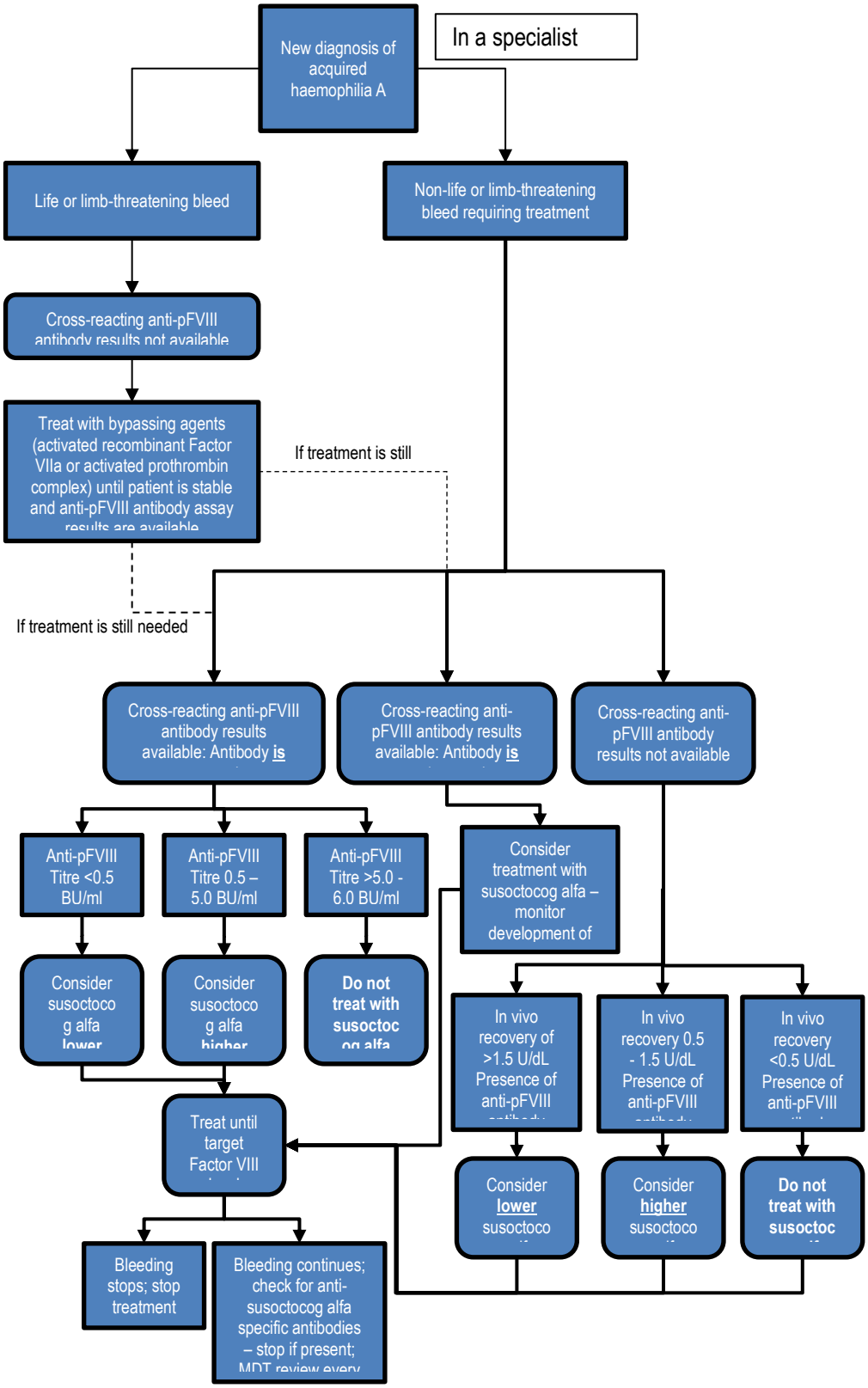


Figure 2 Pathway for patients at a specialist centre



8 Governance Arrangements

The service specification for haemophilia (B05/S/a 2013/14 NHS standard contract for haemophilia [all ages]) describes the care pathways and key aspects being commissioned and should be referred to in conjunction with this policy.
Accurate assessment of anti-FVIII antibody activity is essential to determine the eligibility and assessing the efficacy of susoctocog alfa. This will require clinicians experienced in assessing and treating AHA. Susoctocog alfa should only be prescribed at comprehensive care centres with clinicians experienced in treating AHA. It can be prescribed at haemophilia centres without this expertise in consultation with clinicians experienced in treating AHA from a haemophilia comprehensive care centre.

Any provider organisation treating patients with this intervention will be required to confirm that the internal governance arrangements have been completed before the medicine is prescribed. This should include detailing the process for MDT discussion, for which logistical details may differ between sites. These arrangements may be through the Trust's Drugs and Therapeutics committee (or similar) and NHS England may ask for assurance of this process.

Provider organisations must register all patients with the National Haemophilia Database and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

9 Mechanism for Funding

The funding and commissioning will be managed through the relevant local NHS England Specialised Commissioning Team.

10 Audit Requirements

Specialised centres will be required to ensure that processes are in place to track decision to treat and evidence of effectiveness. Patients with AHA should be registered in the National Haemophilia Database. Centres may use software

systems to track and audit use of susoctocog alfa, in order to ensure it is administered according to the Criteria for Commissioning.

11 Documents which have informed this Policy

The documents that have informed this policy include a review of the clinical evidence available for susoctocog alfa. Additional evidence sources are listed in the table of references below.

12 Date of Review

This document will be reviewed when information is received which indicates that the policy requires revision.

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

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END