NHS England

Clinical Commissioning Policy Proposition:

Emicizumab as prophylaxis in people with congenital haemophilia A with factor VIII inhibitors (all ages)

Reference: NHS England 1717

Prepared by the National Institute for Health and Care Excellence (NICE) Commissioning Support Programme for the Cancer & Blood Programme Clinical Reference Group.

Published by NHS England, in electronic format only.

Contents

1 Executive Summary 4

Equality Statement 4

Plain Language Summary 4

2 Introduction 6

3 Proposed Intervention and Clinical Indication 7

4 Definitions 7

5 Aims and Objectives 8

6 Epidemiology and Needs Assessment 8

7 Evidence Base 10

Effectiveness 10

Safety and tolerability 13

Grade of evidence and limitations of the evidence ..... **Error! Bookmark not defined.**

8 Proposed Criteria for Commissioning 15

9 Proposed Patient Pathway 18

10 Proposed Governance Arrangements 18

11 Proposed Mechanism for Funding 19

12 Proposed Audit Requirements 19

13 Documents That Have Informed This Policy Proposition 19

14 Date of Review 20

15 References 21

1 Executive Summary

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 haemophilia A (with factor VIII inhibitors)

Haemophilia A is a rare condition that affects the blood's ability to clot. Haemophilia A is usually inherited and usually occurs in males. Instances in females are rare.

Normally, when a person cuts themselves, substances in the blood called clotting factors combine with blood cells called platelets, making the blood clot and stopping the bleeding. People with haemophilia A do not have enough of a clotting factor called factor VIII (eight) in their blood, or it isn't working properly. This means they cannot form strong clots and so they bleed for longer than usual.

Symptoms of haemophilia A can be mild to severe, depending on the level of clotting factor VIII. People with haemophilia A may bruise easily and bleed for longer than people who do not have haemophilia A. Bleeding can be external (for example, from cuts) or internal (for example, into the brain or into joints, including the knee and elbow). Bleeding into joints causes acute pain and over time irreversible damage to

the joints (reducing the person's ability to move) and reduce the person's quality of life. Bleeding into the brain may be fatal.

People with severe haemophilia A are normally treated by replacing the missing factor VIII. Factor VIII replacement treatment prevents bleeds and allows the person to grow up with normal joints. Sometimes the body's immune system sees the replacement factor VIII as 'invading' the body. The body produces antibodies called 'inhibitors' to attack the replacement factor VIII, stopping it from working. This happens to around 1 in 3 people with severe haemophilia A who are treated with replacement factor VIII. Compared to people without inhibitors, people with inhibitors have a higher rate of bleeding complications (bleeds are harder to prevent and to treat) and are more likely to have joint damage.

About current treatments

There is currently no cure for haemophilia A. Lifelong treatment is required. The aim of treatment for haemophilia A is to prevent bleeding episodes from occurring. In particular, the aim is to prevent joint bleeds (and therefore prevent joint damage) and other serious bleeds which can lead to disability and death. Bleeds can be prevented by injections of factor VIII given 3 to 4 times a week, however, this treatment is not possible for people with an inhibitor because the factor VIII does not work.

One of the main treatments for people with haemophilia A with factor VIII inhibitors is to try to eradicate the inhibitors, using a treatment called immune tolerance induction (ITI). NHS England has produced a policy about this treatment: NHS England Clinical Commissioning Policy: Immune Tolerance Induction [ITI] for haemophilia A. About two-thirds of patients who develop an inhibitor can be expected to achieve inhibitor eradication following ITI.

People with an inhibitor who cannot be treated with factor VIII are treated with "bypassing agents" – these activate the blood clotting system differently to factor VIII and are not affected by inhibitors. However, bypassing agents are not as good as factor VIII for preventing or treating bleeds. Bypassing agents are given by injection into a vein, or into a central venous access devices (CVADs) which facilitates venous access. The 2 main ways of giving bypassing agents are:

- Preventative treatment (also called prophylaxis) – the person has regular bypassing agent injections (every 2-3 days) to prevent or reduce the risk of bleeding. About two-thirds of people with haemophilia A with inhibitors in the UK are managed with a prophylactic bypassing agent regimen.

- On-demand treatment (also called episodic treatment) – the person has bypassing agent injections only when a bleed occurs to stop the bleed. About one-third of people with haemophilia A and inhibitors in the UK are managed with an on-demand bypassing agent regimen.

About the new treatment

Emicizumab is a drug used to prevent bleeding or reduce the number of bleeds in people with haemophilia A who have factor VIII inhibitors. It is administered as a subcutaneous injection. Emicizumab works by binding to factor X and activated factor IX which brings those clotting factors near each other and activates the blood clotting system even if no factor VIII is present. This is different to how replacement factor VIII and bypassing agents work. Emicizumab is injected under the skin (subcutaneous injection) once a week. The dose given depends on the patient's weight.

What we have decided

NHS England has carefully reviewed the evidence to prevent or reduce the frequency of bleeding episodes in people with haemophilia A who have factor VIII inhibitors with emicizumab. We have concluded that there is enough evidence to consider making the treatment available.

2 Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to routinely commission emicizumab as prophylaxis in people with congenital haemophilia A with factor VIII inhibitors.

This document also describes the proposed criteria for commissioning, proposed governance arrangements and proposed funding mechanisms.

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether emicizumab will be routinely commissioned for this indication will be made by NHS England following a recommendation from the Clinical Priorities Advisory Group.

3 Proposed Intervention and Clinical Indication

People with haemophilia A have deficient clotting factor VIII activity, placing them at risk of spontaneous and traumatic bleeding events. Regular replacement of the missing factor VIII to prevent bleeds is the standard of care for people with haemophilia A who have a severe bleeding phenotype. However, approximately one-third of people who receive factor VIII replacement therapy will develop factor VIII inhibitors which make the replacement factor VIII ineffective.

Treatments for people with haemophilia A with factor VIII inhibitors include the eradication of the inhibitors (through immune tolerance induction [ITI]), or bleeds may be prevented or treated with treatments that activate the blood clotting system by bypassing the inhibitors. These treatments are called bypassing agents. The bypassing agents that are currently available are recombinant factor VIIa and activated prothrombin complex concentrate. Bypassing agents can be given as episodic (on-demand) treatment if a bleed has occurred or as prophylactic treatment to reduce or prevent bleeding. At the time of this review the only bypassing agent licensed for prophylaxis in people with haemophilia A is activated prothrombin complex concentrate.

Emicizumab works by linking activated factor IX and factor X to activate the blood clotting system in the absence of factor VIII.

4 Definitions

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)
Antibody	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
Arthropathy	A disease of a joints
Bethesda units	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
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
Haemophilia A	An inherited condition, affecting predominately males, in which there is excessive bleeding which can follow trauma or can occur spontaneously due to insufficient production of factor VIII, an essential blood-clotting protein
Inhibitor	An antibody produced by the immune system which neutralises and de-activates factor VIII
Inhibitor titres	Measured in Bethesda units (BU). The higher the number of Bethesda units, the more inhibitors are present
rFVIIa	An activated form of factor VII which bypasses factors VIII and IX and stops bleeding without the need for factor VIII
Target joint	A joint in the body where there have been at least 3 bleeds in the last 6 months
Antibody titre	The amount of antibody) in the bloodstream

5 Aims and Objectives

This policy proposition considered: emicizumab as prophylaxis in people with congenital haemophilia A with factor VIII inhibitors (all ages).

The objectives were to:

- ensure evidence based commissioning with the aim of improving outcomes for patients with haemophilia A with factor VIII inhibitors; and
- identify clinical criteria for treating patients with haemophilia A with factor VIII inhibitors.

6 Epidemiology and Needs Assessment

The UK National Haemophilia Database Bleeding Disorder Statistics for 2015-2016 reports that between April 2015 and March 2016 there were 5,930 people in the UK

with mild, moderate or severe forms of haemophilia A (not including low-level carriers; factor VIII level <40 IU/dL). Of these, 230 people (3.9%) have current inhibitors, the majority of whom have severe haemophilia A (164 people; 71%), followed by moderate (42 people; 18%) and mild (24 people; 10%). For this time period there were 29 people with haemophilia A who had newly reported inhibitors (excluding low-level carriers). Of these 19 people (66%) had severe haemophilia A, 4 people (14%) had moderate and 6 people (21%) had mild.

The eligible patient population for emicizumab in the UK is considered to be equivalent to the patients with current inhibitors (n=230).

England specific data for 2016/17 was obtained from the UK National Haemophilia Database and shows that there were 177 existing patients in England with congenital haemophilia A and inhibitors and there 24 patients with congenital haemophilia A who were newly identified as having inhibitors.

Permanent joint damage: About 90% of people with severe haemophilia experience long-term worsening changes in major joints. This is called haemophilic arthropathy and is one of the main challenges in managing haemophilia A. These changes can happen in one to six joints (ankles, elbows, knees). Joint damage starts at a young age and usually becomes clinically significant when the person is in their teens or 20s (O'Hara et al., 2017). Patients with haemophilia A with inhibitors have a higher level of lifelong arthropathy and more severe joint problems than patients without inhibitors (Jimenez-Yuste et al. 2008).

Bleeding: Bypassing agents are variable in their ability to control bleeding with between 85% and 97% efficacy at 48 hours (Astermark et al. 2007). People with inhibitors are at a greater risk of bleeds, have more frequent hospital admissions due to bleeding in muscles or joints, and have worse overall outcomes of joint bleeding than people without inhibitors. (Brown et al. 2009) (Morfini et al. 2007).

Method of administration: Bypassing agents (aPCC and rFVIIa) can only be given intravenously which can cause pain and stress and requires frequent access to veins: this may be difficult for some patients to maintain long-term. As a result, children and young adults with haemophilia A with factor VIII inhibitors often require central venous access devices (CVADs) to be inserted surgically. CVADs allow

easier treatment administration of bypassing agents but having a CVAD increases the risk of infection and thrombosis (Rodriguez et al., 2015). In addition to the known increased risk of thrombosis associated with bypassing agents, the use of bypassing agents can block a CVAD which requires the use of anticoagulants to clear the blockage. Emicizumab is administered subcutaneously, removing the need for venous access.

Dose frequency: Bypassing agents have a short half-life (a few hours), thus requiring injections into veins every 2-3 days to prevent bleeds and up to every 2 hours to treat bleeds. Emicizumab has a long half-life and is administered once a week.

7 Evidence Base

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

The evidence for the efficacy and safety of emicizumab came from 1 study that was included in the clinical; evidence review.

Oldenburg et al. 2017 was a 24-week, open-label, phase III, randomised trial in 109 people (53 randomised and 56 non-randomised) with haemophilia A with factor VIII inhibitors (median age 28 years [range 12 to 75]; 29% aged less than 18 years). (NCT02476942).

Effectiveness

Bleeding outcomes

The primary efficacy outcome in the study by Oldenburg et al. (2017) was number of bleeds requiring treatment with a bypassing agent. People previously treated with episodic bypassing agents who received emicizumab had a lower annualised treated bleed rate (Group A, 2.9 events, 95% CI 1.7 to 5.0) compared with no prophylaxis (episodic treatment only) (Group B, 23.3 events, 95% Confidence Interval (CI) 12.3 to 43.9; risk ratio [RR] 0.13, 95% CIs not reported; p<0.001). These results suggest that compared with no prophylaxis treatment (episodic

treatment only), emicizumab reduced the number of bleeds requiring treatment per year by 87%.

For people who had previously received prophylactic treatment with a bypassing agent (group C, n=49) the annualised treated bleed rate was 5.1 events (95% CI 2.3 to 11.2). This study was not designed to compare group C to the no prophylaxis (episodic treatment only) group B and therefore statistical analyses are not reported.

Statistically significant reductions in annualised bleeding rates for emicizumab (group A) compared with no prophylaxis (group B) were also observed for the secondary bleeding-related outcomes: all bleeds (RR 0.20), spontaneous bleeds (RR 0.08) and joint bleeds (RR 0.11, all p<0.01).

Health-related quality of life and health status outcomes

Health-related quality of life was reported using the Haemophilia Quality of Life Questionnaire (Haem-A-QoL) physical health subscale and total score. The Haem-A-QoL assesses health-related quality of life in people with haemophilia A and B. The questionnaire consists of 46 items and is composed of 10 subscales; all subscales are combined to get a total score. Subscale scores are transformed to a 0 to 100 scale, with lower scores suggesting better health-related quality of life. A reduction of 10 points on the physical health subscale and 7 points in total score represent a clinically meaningful improvement in health-related quality of life (Wyrwich et al. 2015).

At week 25 the adjusted mean difference in the Haem-A-QoL physical health subscale between emicizumab (group A) and no prophylaxis (group B) was 21.6 points (95% CI 7.9 to 35.2, p=0.003). This mean reduction is greater than the minimal clinically meaningful difference (MCID) of 10 points. The lower limit of the 95% CI fell below the MCID. Similar results were observed for the Haem-A-QoL total score, with a mean reduction greater than the MCID of 7 points observed. Again the lower limit of 95% CI fell below the MCID (adjusted mean difference 14.0 points, 95% CI 5.6 to 22.4, p=0.002).

Health status was reported using the 5-level version of the EuroQol group 5-Dimension Self-Report Questionnaire (EQ-5D-5L) visual analogue scale and index

utility score. EQ-5D is a standardised instrument for measuring health status that can be used in a wide range of health conditions and treatments. The EQ-5D-5L visual-analogue scale ranges from 0 to 100, with higher scores indicating better health status and a change of 7 points is considered a clinically meaningful difference (Pickard et al. 2007). The EQ-5D-5L index utility score ranges from −0.4 to 1.0, with higher scores indicating better health status and a change of 0.07 points is considered a clinically meaningful difference (Pickard et al. 2007).

At week 25 the adjusted mean difference in the EQ-5D-5L visual-analogue scale between emicizumab (group A) and no prophylaxis (group B) was −9.7 points (95% CI −17.6 to −1.8, p=0.02). The mean reduction was greater than the MCID of 7 points. The lower limit of the 95% fell below the MCID. Significant reductions were also reported for the EQ-5D-5L index utility score (−0.16 points, 95% CI −0.25 to −0.07, p=0.001). The mean reduction is greater than the MCID of 0.07 points. The lower limit of the 95% CI fell below the MCID.

Before-and-after comparison

Oldenburg et al. (2017) also reported intra-individual comparisons of emicizumab with standard care in a sub-set of participants previously recruited into a non-interventional study. In total 24 participants in group A (who were previously treated episodically) and 24 participants in group C (who were previously treated prophylactically) had been recruited into a prospective, non-interventional study that collected real-world data on bleeding events and safety outcomes in people with haemophilia A who received episodic or prophylactic treatment with bypassing agents (given according to local, routine clinical practice). This non-interventional study has not been published in a peer-reviewed journal, although some results are reported by Oldenburg et al. (2017).

Among the people in group C who took part in the non-interventional study (n=24), the intra-individual comparison showed a significantly lower annualised bleeding rate with emicizumab (3.3 events, 95% CI 1.3 to 8.1) compared with previous treatment with prophylactic bypassing agents (15.7 events, 95% CI 11.1 to 22.3). This is a 79% reduction in bleeding rate (p<0.001, 95% CIs not reported).

Among the 24 people in group A who took part in the non-interventional study, the

annualised bleeding rate was significantly lower with emicizumab (1.7 events, 95% CI 0.7 to 4.1) compared with previous episodic bypassing agents (21.6 events, 95% 15.4 to 30.2). This is a 92% reduction in bleeding rate (p<0.001, 95% CI not reported).

The results of this intra-individual comparison need to be interpreted with care. The non-interventional study has not yet been published in a peer-reviewed journal, meaning there are no details on baseline characteristics and the treatments the participants received. It is not clear from the report by Oldenburg et al. how participants were selected from the non-interventional study, and whether selection bias may be present. In addition to this, care must be taken when comparing the results of a 'real-world' study using standard-care with the results of a more rigidly controlled clinical trial. In the absence of a published study these results cannot be critically appraised.

Safety and tolerability

Adverse events

In total, 198 adverse events were reported in 103 participants receiving emicizumab in the study by Oldenburg et al. (2017); this includes people in the no prophylaxis group who were switched to emicizumab after week 25 (n=13). Across the 4 treatment arms, during treatment with emicizumab 73 out of 103 people (70.9%) reported 1 or more adverse events. The most common adverse event was injection-site reactions (28 events in 15 people). In addition to this 9 people reported an upper respiratory tract infection, 12 people reported headache, 6 people reported fatigue and 6 people reported arthralgia (number of actual events not reported). These common adverse events were all mild in intensity and resolved, except for 1 case of moderate injection-site haematoma occurring on day 2 of the trial, which resolved on day 28.

Serious adverse events during emicizumab treatment were reported in 9 out of 103 (8.7%) people. Cases of thrombotic microangiopathy (in 2 participants), skin necrosis and superficial thrombophlebitis (in 1 participant) and cavernous sinus thrombosis (in 1 participant) were reported in people who had received multiple

infusions of activated prothrombin complex concentration while receiving emicizumab. The cases of thrombotic microangiopathy resolved after the activated prothrombin complex concentrate was stopped, and neither thrombotic events required anticoagulation. The authors report that after data cut-off for the primary analysis, thrombotic microangiopathy developed in 1 additional participant. This occurred 5 days after their previous emicizumab dose and after 4 consecutive days of treatment with activated prothrombin complex concentration which was given for a rectal haemorrhage. This rectal bleeding was recurrent and eventually fatal; although the investigators assessed that the thrombotic microangiopathy was resolved at the time of death. Other serious adverse events reported during emicizumab prophylaxis included iron deficiency anaemia, sepsis, haemarthrosis, muscle haemorrhage, gastric ulcer haemorrhage, headache and haematuria (occurring in 1 participant each).

The investigators report that of 104 participants receiving emicizumab, 28 people (27%) used activated prothrombin complex concentrate, 34 people (33%) used recombinant factor VIIa, and 13 people (12%) used both bypassing agents. A range of doses for recombinant factor VIIa were used, and most treatment episodes lasted for 1 day. Most people treated with activated prothrombin complex concentrate received doses less than 100 U/kg for 1 day, although in 19 treatment events a dose of more than 100 U/day was given for more than 1 day. All of the 5 people who had thrombotic microangiopathy or thrombosis had received activated prothrombin complex concentration at a dose of more than 100 U/kg for more than 1 day. The maximum licenced dose of activated prothrombin complex concentrate to treat bleeds is 200 U/kg/d.

The investigators note that when aPCC and emicizumab are given at the same time, emicizumab has more factor IX and X molecules to bind to. This along with other activated and non-activated coagulation factors that have half-lives of up to 60 hours can accumulate with multiple doses. The combination of emicizumab and aPCC could increase the risk of adverse effects such as the microangiopathy observed during the trial, therefore the use of both treatments at the same time should only be undertaken if clinical necessary, i.e. a bleed has failed to respond to rFVIIa, and under the 24 hour supervision of a haematologist with expertise in treating

haemophilia at a comprehensive care centre.

Pharmacokinetics and antibodies

No participants tested positive for anti-drug antibodies for emicizumab. However, the pharmacokinetic profiles of 2 participants showed declining exposure to emicizumab over-time, which may be suggestive of anti-drug antibodies. One of these participants experienced no bleeding events while on emicizumab prophylaxis, and the other is being monitored after having their dose of emicizumab increased to 3 mg/kg at week 24 (shortly before the primary analysis). Both participants remained in the trial and are being followed up.

8 Proposed Criteria for Commissioning

NHS England will routinely commission emicizumab prophylaxis in adults and children with congenital haemophilia A and inhibitors to prevent bleeding episodes where the patient :

- Has a factor VIII inhibitor confirmed on more than one occasion by a Nijmegen-modified Bethesda assay, that compromises the effect of prophylaxis or treatment of bleeds at standard doses of factor VIII

AND meets at least one of the following criteria:

- has had ITI if indicated (as per NHS England policy) which has not been successful in eradicating the inhibitor (see section 9); OR
- is an existing patient with poorly controlled bleeding episodes; OR
- currently receives bypassing agents either prophylactically or on-demand; OR
- is undergoing ITI and requires prophylaxis to prevent breakthrough bleeding episodes during ITI treatment.

Emicizumab will only be commissioned and funded via Haemophilia Comprehensive Care Centres.

Patients, or their carers, must be trained in the storage, handling and administration of emicizumab and satisfy clinical teams of their competence in these respects.

Patients will receive their medication via an approved homecare service and must comply with the requirements of the service.

When emicizumab is initiated patients should be advised to identify the emergence of any delayed allergic reactions or injection site reactions.

Patients, or their carers, must be shown how to identify the emergence of any thrombotic events during treatment with emicizumab.

Patients, or their carers, must provide their clinical team with data pertaining to dose administration and related clinical sequelae such as bleeding episodes. This is most easily achieved through the use of a secure therapy recording digital interface.

During treatment

Bleeding episodes which occur during treatment with emicizumab must be managed by a Haemophilia Comprehensive Care Centre that has facilities for 24 hour in-patient care for managing bleeding episodes.

Initial management of a bleeding episode in the context of emicizumab prophylaxis should be through the use of rFVIIa.

If bleeding is inadequately controlled then treatment with aPCC should be considered, but only under the direct guidance of a Haemophilia Comprehensive Care Centre and in accordance with guidelines from the UK Haemophilia Centres Doctors' Organisation and British Society for Haematology. (Hanley et al. 2017.)

Patients and clinicians should be advised that the following tests are affected by the presence of emicizumab :

- Activated partial thromboplastin time (aPTT)
- Bethesda assays (clotting-based) for FVIII inhibitor titres
- One-stage, aPTT-based, single-factor assays
- aPTT-based Activated Protein C Resistance (APC-R)
- Activated clotting time (ACT)

Clinicians will need to conduct alternative tests if any of these parameters are required.

Patients will not normally hold or possess more than 3 months of medication at any one time.

Stopping Criteria:

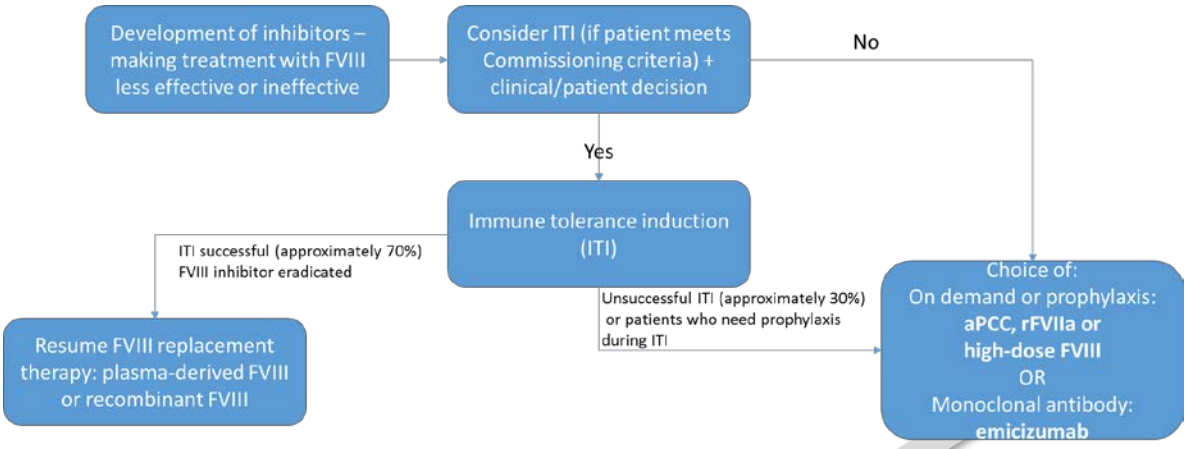
Treatment with emicizumab should be withdrawn and ceased in the following situations:

- An increase in the number of bleeding episodes compared with previous treatment
- Less than 50% reduction in number of breakthrough bleeds after 6 months of maintenance prophylaxis with emicizumab compared with previous episodic (on-demand) treatment.

The decision to continue with treatment in the following situations must be undertaken by an appropriate Haemophilia MDT to balance the risks and benefits:

- A thrombotic event or other significant adverse reaction occurs or any major comorbidity arises or is identified during treatment (e.g. malignancy)
- Neutralising antibodies to emicizumab are identified
- An elective surgical procedure is required.

9 Proposed Patient Pathway



*Treatment with emicizumab can be considered for patients for whom ITI was not an option or for patients who have undergone ITI and it has not been successful. Some patients who are having ITI may need prophylaxis to prevent bleeding during that treatment. Emicizumab can also be considered for those patients.

10 Proposed Governance Arrangements

Each provider organisation treating children with a medicine approved under this policy will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Trust's Drugs and Therapeutics Committee (or similar) and NHS England can ask for documented evidence that these processes are in place.

Provider organisations must register all patients using software to monitor bleeds (a secure therapy recording system) and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

Patients with factor VIII inhibitors must be registered with, and have their treatment co-ordinated by a haemophilia comprehensive care centre experienced in the management of inhibitors in accordance with the 2013/14 NHS Standard Contract for Haemophilia (all ages). In line with the NHS England service specification for specialised haemophilia services, centres must provide 24 hour access to senior clinicians with experience in inhibitor management and laboratory services for the

measurement of factor levels and inhibitor titres.

Treatment with emicizumab should be initiated and monitored under the supervision of a physician experienced in the treatment of haemophilia and/or bleeding disorders at a comprehensive care haemophilia centre.

11 Proposed Mechanism for Funding

The funding and commissioning will be managed through the relevant local NHS England Specialised Commissioning Team. Emicizumab is listed as a tariff-exempt medicine.

12 Proposed Audit Requirements

All patients must be registered with the UK National Haemophilia Database and details of their inhibitor reported as soon as they are confirmed. The outcome of emicizumab prophylaxis must be reported to the National Haemophilia Database annually. Patients receiving emicizumab must record all their bleeds and treatment on a secure therapy recording system.

All haemophilia comprehensive care centres will be required to participate in national audits, which will include:

- starting dose and dose changes to review compliance with protocols
- Factor VIII and bypassing agent usage
- Number of bleeding episodes per year (and annualised baseline number of bleeding episodes before commencing emicizumab prophylaxis)
- Adverse reactions (including thrombotic events and allergic reactions)

13 Documents That Have Informed This Policy Proposition

The documents that have informed this policy proposition include a review of the clinical evidence available for emicizumab and the following:
NHS England. (2016) The standard service model for haemophilia services was set out in the Health Service Guidance HSG (93) 30 ‘Provision of Haemophilia

Treatment and Care'. This stated that there should be two different levels of haemophilia provision:

- Comprehensive Care Centres (CCCs) provide specialist diagnosis and care
- Haemophilia Centres (HCs) provide a local, shared care service

This includes services delivered on an outreach basis as part of a provider network. NHS England (2013) A service specification for haemophilia services commissioned by NHS England has been developed (B05/S/a). The specification notes that CCCs will normally provide treatment for 40 or more severely affected patients per year. NHS England (2016) CQUIN for 2017 - 2019 to encourage improved adherence, timeliness, and accuracy of patient data submissions to a secure therapy recording system.

Additional evidence sources are listed in the table of references below.

14 Date of Review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned.

15 References

Alliance, H. 2006. *A National Service Specification for Haemohilia and Other Inherited Bleeding Disorders* [Online]. Available: http://www.ukhcdo.org/docs/HaemAlliance-NatSvsSpec2006.pdf.

Astermark, J., Donfield, S. M., Dimichele, D. M., Gringeri, A., Gilbert, S. A., Waters, J., Berntorp, E. & Group, F. S. 2007. A randomized comparison of bypassing agents in hemophilia complicated by an inhibitor: the FEIBA NovoSeven Comparative (FENOC) Study. *Blood,* 109**,** 546-51.

Baxalta Innovations GMBH. *FEIBA 500 U powder and solvent for solution for infusion: Summary of Product Characteristics* [Online]. Available: http://www.medicines.org.uk/emc/medicine/30169 [Accessed 05 July 2017.

Blanchette, V. S., Key, N. S., Ljung, L. R., Manco-Johnson, M. J., Van Den Berg, H. M., Srivastava, A., Subcommittee On Factor VIII, F. I. X., Rare Coagulation Disorders of the, S., Standardization Committee of the International Society on, T. & Hemostasis 2014. Definitions in hemophilia: communication from the SSC of the ISTH. *J Thromb Haemost,* 12**,** 1935-9.

Brown, T. M., Lee, W. C., Joshi, A. V. & Pashos, C. L. 2009. Health-related quality of life and productivity impact in haemophilia patients with inhibitors. *Haemophilia,* 15**,** 911-7.

Collins, P. W., Chalmers, E., Hart, D., Jennings, I., Liesner, R., Rangarajan, S., Talks, K., Williams, M., Hay, C. R. M. & United Kingdom Haemophilia Centre Doctors, O. 2013a. Diagnosis and management of acquired coagulation inhibitors: a guideline from UKHCDO. *Br J Haematol,* 162**,** 758-73.

Collins, P. W., Chalmers, E., Hart, D. P., Liesner, R., Rangarajan, S., Talks, K., Williams, M., Hay, C. R. & Doctors, U. K. H. C. 2013b. Diagnosis and treatment of factor VIII and IX inhibitors in congenital haemophilia: (4th edition). UK Haemophilia Centre Doctors Organization. *Br J Haematol,* 160**,** 153-70.

Hanley, J., Mckernan, A., Creagh, M. D., Classey, S., Mclaughlin, P., Goddard, N., Briggs, P. J., Frostick, S., Giangrande, P., Wilde, J., Thachil, J., Chowdary, P. & Musculoskeletal Working Party of the, U. 2017. Guidelines for the management of acute joint bleeds and chronic synovitis in haemophilia: A United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) guideline. *Haemophilia,* 23**,** 511-520.

Hay, C. R., Brown, S., Collins, P. W., Keeling, D. M. & Liesner, R. 2006. The diagnosis and management of factor VIII and IX inhibitors: a guideline from the United Kingdom Haemophilia Centre Doctors Organisation. *Br J Haematol,* 133**,** 591-605.

Jimenez-Yuste, V., Rodriguez-Merchan, E. C., Alvarez, M. T., Quintana, M., Martin-Salces, M. & Hernandez-Navarro, F. 2008. Experiences in the prevention of arthropathy in haemophila patients with inhibitors. *Haemophilia,* 14 Suppl 6**,** 28-35.

Keeling, D., Tait, C. & Makris, M. 2008. Guideline on the selection and use of therapeutic products to treat haemophilia and other hereditary bleeding disorders. A United Kingdom Haemophilia Center Doctors' Organisation (UKHCDO) guideline approved by the British Committee for Standards in Haematology. *Haemophilia,* 14**,** 671-84.

Morfini, M., Haya, S., Tagariello, G., Pollmann, H., Quintana, M., Siegmund, B., Stieltjes, N., Dolan, G. & Tusell, J. 2007. European study on orthopaedic status of haemophilia patients with inhibitors. *Haemophilia,* 13**,** 606-12.

NHS England. 2013. *NHS standard contract for haemophilia (all ages) B05/S/a.* [Online]. Available: https://www.england.nhs.uk/wp-content/uploads/2013/06/b05-haemophilia.pdf.

NHS England. 2016. *Revised specialised commissioning CQUINs 2016-17 2017-18.* [Online]. Available: https://www.england.nhs.uk/wp-content/uploads/2016/11/pss-cquin-schemes.pdf.

NHS England Specialised Commissioning Team. 2016. *Clinical Commissioning Policy. Immune tolerance induction (ITI) all ages* [Online]. NHS England. Available: https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/07/16042_FINAL.pdf [Accessed 05 July 2017.

NHS England. 2016. *NHS England. Manual for prescribed specialised services 2016-17.* [Online]. Available: https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2016/06/pss-manual-may16.pdf.

Novonordisk A/S NovoSeven powder and solvent for solution for injection: Summary of Product Characteristics.

O'hara, J., Hughes, D., Camp, C., Burke, T., Carroll, L. & Diego, D. G. 2017. The cost of severe haemophilia in Europe: the CHESS study. *Orphanet J Rare Dis,* 12**,** 106.

Oldenburg, J., Mahlangu, J. N., Kim, B., Schmitt, C., Callaghan, M. U., Young, G., Santagostino, E., Kruse-Jarres, R., Negrier, C., Kessler, C., Valente, N., Asikanius, E., Levy, G. G., Windyga, J. & SHIMA, M. 2017. Emicizumab Prophylaxis in Hemophilia A with Inhibitors. *N Engl J Med*.

Richards, M., Williams, M., Chalmers, E., Liesner, R., Collins, P., Vidler, V., Hanley, J. & Paediatric Working Party Of The United Kingdom Haemophilia Doctors, O. 2010. A United Kingdom Haemophilia Centre Doctors' Organization guideline approved by the British Committee for Standards in Haematology: guideline on the use of prophylactic factor VIII concentrate in children and adults with severe haemophilia A. *Br J Haematol,* 149**,** 498-507.

Rodriguez, V., Mancuso, M. E., Warad, D., Hay, C. R., Dimichele, D. M., Valentino, L., Kenet, G. & Kulkarni, R. 2015. Central venous access device (CVAD) complications in Haemophilia with inhibitors undergoing immune tolerance induction: Lessons from the international immune tolerance study. *Haemophilia,* 21**,** e369-74.

Srivastava, A., Brewer, A. K., Mauser-Bunschoten, E. P., Key, N. S., Kitchen, S., Llinas, A., Ludlam, C. A., Mahlangu, J. N., Mulder, K., Poon, M. C., Street, A. & Treatment Guidelines Working Group on behalf of the World Federation of, H. 2013. Guidelines for the management of hemophilia. *Haemophilia,* 19**,** e1-47.

UKHCDO 2017. UKHCDO protocol for first line immune tolerance induction for children with severe haemophilia A: A protocol from the UKHCDO Inhibitor and Paediatric Working Parties. Available http://www.ukhcdo.org/wp-content/uploads/2017/01/ITI-protocol-2017.pdf [Accessed 06 Dec 2017].

UKHCDO National Haemophilia Database. 2016. *Bleeding Disorder Statistics for 2015-2016* [Online]. Available: http://www.ukhcdo.org/wp-content/uploads/2017/03/Bleeding-Disorder-Statistics-for-April-2015-to-March-2016-for-UKHCDO-Website.pdf [Accessed 06 Dec 2017].

UKHCDO National Haemophilia Database 2017. Roche and Chugai UK Needs: Preliminary Report.

White, G. C., 2nd, Rosendaal, F., Aledort, L. M., Lusher, J. M., Rothschild, C., Ingerslev, J., Factor, V. & Factor, I. X. S. 2001. Definitions in hemophilia. Recommendation of the scientific subcommittee on factor VIII and factor IX of the scientific and standardization committee of the International Society on Thrombosis and Haemostasis. *Thromb Haemost,* 85**,** 560.

END