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Welsh Health Specialised Services Committee (WHSSC)

Specialised Services Policy Position PP167

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

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Description	NHS Wales will routinely commission this specialised service in accordance with the criteria described in this policy
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Contents

Policy Statement

Welsh Health Specialised Services Committee (WHSSC) will commission Emicizumab as prophylaxis treatment for people with congenital haemophilia A with factor VIII inhibitors in accordance with the criteria outlined in this document.

In creating this policy, WHSSC has reviewed the relevant guidance issued by NHS England and has concluded that Emicizumab as prophylaxis treatment for people with congenital haemophilia A with factor VIII inhibitors should be made available to patients in Wales.

This WHSSC policy position adopts the commissioning criteria of the NHS England commissioning policy, Emicizumab as prophylaxis in people with congenital haemophilia A with factor VIII inhibitors (all ages)[1].

Disclaimer

WHSSC assumes that healthcare professionals will use their clinical judgment, knowledge and expertise when deciding whether it is appropriate to apply this policy position statement.

This policy may not be clinically appropriate for use in all situations and does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

WHSSC disclaims any responsibility for damages arising out of the use or non-use of this policy position statement.

[1] https://www.england.nhs.uk/wp-content/uploads/2018/07/1717-emicizumab.pdf

1. Introduction

This Policy Position has been developed for the planning and delivery of Emicizumab as prophylaxis treatment for people with congenital haemophilia A with factor VIII inhibitors for people resident in Wales. This proposed service will only be commissioned by the Welsh Specialised Services Committee (WHSSC) and applies to residents of all seven Health Boards in Wales.

1.1 Plain language summary

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.

1.2 Aims and Objectives

This Policy Position Proposal aims to define the commissioning position of WHSSC on the use of Emicizumab as prophylaxis treatment for people with congenital haemophilia A with factor VIII inhibitors.

The objectives of this policy are to:

- ensure commissioning for the use of Emicizumab is evidence based

- ensure equitable access to Emicizumab
- define criteria for people with congenital haemophilia A with factor VIII inhibitors to access treatment
- improve outcomes for people with congenital haemophilia A with factor VIII inhibitors

1.3 Epidemiology

The UK National Haemophilia Database Bleeding Disorder Statistics[2] 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).

1.4 Current Treatment

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). 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 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

[2] http://www.ukhcdo.org/wp-content/uploads/2017/07/Bleeding_Disorder_Statistics_for_April_2015_-March_016-forUKHCDO_Wbsite_V2.pdf

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.

1.5 Proposed 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.

1.6 What NHS Wales has decided

WHSSC has carefully reviewed the relevant guidance issued by NHS England. We have concluded that there is enough evidence to fund the use of Emicizumab as prophylaxis treatment for people with congenital haemophilia A with factor VIII inhibitors within the criteria set out in section 2.2.

2. Criteria for Commissioning

The Welsh Health Specialised Services Committee propose to approve funding of Emicizumab as prophylaxis treatment for people with congenital haemophilia A with factor VIII inhibitors in-line with the criteria identified in the policy.

2.1 Introduction

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.

2.2 Inclusion Criteria

WHSSC 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 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.

2.3 Exclusion Criteria

WHSSC will only commission Emicizumab prophylaxis for patients meeting the criteria in 2.2.

2.4 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.

2.5 Continuation of Treatment

Healthcare professionals are expected to review a patient's health at regular intervals to ensure they are demonstrating an improvement to their health due to the treatment being given.

If no improvement to a patient's health has been recorded then clinical judgement on the continuation of treatment must be made by the treating healthcare professional.

2.6 Acceptance Criteria

The service outlined in this specification is for patients ordinarily resident in Wales, or otherwise the commissioning responsibility of the NHS in Wales. This excludes patients who whilst resident in Wales, are registered with a GP practice in England, but includes patients resident in England who are registered with a GP Practice in Wales.

2.7 Patient Pathway (see annex i)

Emicizumab will only be commissioned and funded via Haemophilia Comprehensive Care Centres. Emicizumab should only be prescribed by a Comprehensive Care Centre. All patients receiving Emicizumab must have access 24 hours a day, 7 days a week to consultant haematologists with expertise in treating patients with inhibitors.

2.8 Exceptions

If the patient does not meet the criteria for treatment as outlined in this policy, an Individual Patient Funding Request (IPFR) can be submitted for consideration in line with the All Wales Policy: Making Decisions on Individual Patient Funding Requests. The request will then be considered by the All Wales IPFR Panel.

If the patient wishes to be referred to a provider outside of the agreed pathway, and IPFR should be submitted.

Further information on making IPFR requests can be found at: Welsh Health Specialised Services Committee (WHSSC) | Individual Patient Funding Requests

2.9 Clinical Outcome and Quality Measures

The Provider must work to written quality standards and provide monitoring information to the lead commissioner.

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)

The centre must enable the patient's, carer's and advocate's informed participation and to be able to demonstrate this. Provision should be made for patients with communication difficulties and for children, teenagers and young adults.

2.10 Responsibilities

Referrers should:

- inform the patient that this treatment is not routinely funded outside the criteria in this policy, and
- refer via the agreed pathway.

Clinician considering treatment should:

- discuss all the alternative treatment with the patient;
- advise the patient of any side effects and risks of the potential treatment
- inform the patient that treatment is not routinely funded outside of the criteria in the policy, and
- confirm that there is contractual agreement with WHSSC for the treatment.

In all other circumstances an IPFR must be submitted.

3. Documents which have informed this policy

The following documents have been used to inform this policy:

- **NHS England policies**
  - Clinical Commissioning Policy: Emicizumab as prophylaxis in people with congenital haemophilia A with factor VIII inhibitors (all ages). NHS England Ref:170067/P. July 2018

This document should be read in conjunction with the following documents:

- UK national guidelines on Emicizumab (Collins et al Haemophilia 24:344-347, 2018).

- **NHS Wales**
  - All Wales Policy: Making Decisions in Individual Patient Funding requests (IPFR).

4. Date of Review

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

5. Putting Things Right: Raising a Concern

If the patient does not meet the criteria for treatment as outlined in this policy, an Individual Patient Funding Request (IPFR) can be submitted for consideration in line with the All Wales Policy: Making Decisions on Individual Patient Funding Requests. The request will then be considered by the All Wales IPFR Panel.

If an IPFR is declined by the Panel, a patient and/or their NHS clinician has the right to request information about how the decision was reached. If the patient and their NHS clinician feel the process has not been followed in accordance with this policy, arrangements can be made for an independent review of the process to be undertaken by the patient's Local Health Board. The ground for the review, which are detailed in the All Wales Policy: Making Decisions on Individual Patient Funding Requests (IPFR), must be clearly stated

If the patient wishes to be referred to a provider outside of the agreed pathway, an IPFR should be submitted.

Further information on making IPFR requests can be found at: Welsh Health Specialised Services Committee (WHSSC) | Individual Patient Funding Requests

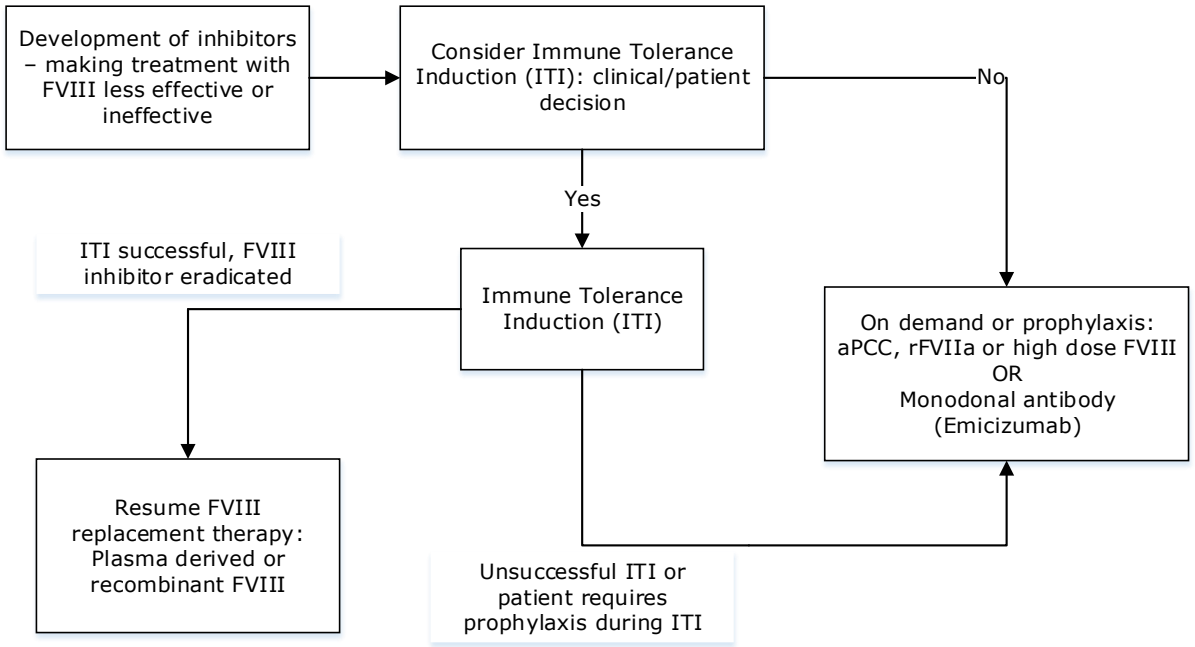
6. Equality Impact and Assessment

The Equality Impact Assessment (EQIA) process has been developed to help promote fair and equal treatment in the delivery of health services. It aims to enable Welsh Health Specialised Services Committee to identify and eliminate detrimental treatment caused by the adverse impact of health service policies upon groups and individuals for reasons of race, gender re-assignment, disability, sex, sexual orientation, age, religion and belief, marriage and civil partnership, pregnancy and maternity and language (Welsh).

This policy has been subjected to an Equality Impact Assessment.

The Assessment demonstrates the policy is robust and there is no potential for discrimination or adverse impact. All opportunities to promote equality have been taken.

Annex i Patient Pathway



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Annex ii Codes

Code Category	Code	Description
ICD-10	D66	Hereditary Factor VIII deficiency

Annex iii Abbreviations and Glossary

Abbreviations

apCC Activated prothrombin complex concentrate

CVAD Central venous access device

IPFR Individual Patient Funding Request

WHSSC Welsh Health Specialised Services

Glossary

Individual Patient Funding Request (IPFR)
An IPFR is a request to Welsh Health Specialised Services Committee (WHSSC) to fund an intervention, device or treatment for patients that fall outside the range of services and treatments routinely provided across Wales.

Welsh Health Specialised Services Committee (WHSSC)
WHSSC is a joint committee of the seven local health boards in Wales. The purpose of WHSSC is to ensure that the population of Wales has fair and equitable access to the full range of Specialised Services and Tertiary Services. WHSSC ensures that specialised services are commissioned from providers that have the appropriate experience and expertise. They ensure that these providers are able to provide a robust, high quality and sustainable services, which are safe for patients and are cost effective for NHS Wales.

Activated prothrombin complex concentrate (apCC)
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.

Antibody titre
The amount of antibody) in the bloodstream.

Arthropathy
A disease of 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 BUs. The higher the number of BUs, 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.