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Clinical Commissioning

Emicizumab for prophylaxis of bleeding episodes in people with moderate haemophilia A without inhibitors (all ages) [URN 2333]

Summary

Emicizumab is recommended to be available as a routine commissioning treatment option for prophylaxis of bleeding episodes in people with moderate haemophilia A without factor VIII inhibitors (all ages) within the criteria set out in this document.

Committee discussion

Clinical Panel recommended that this policy should proceed as a routine commissioning clinical policy. Please see Clinical Panel reports for full details of Clinical Panel's discussion.

The Clinical Priorities Advisory Group are asked to consider the evidence and the policy. The Clinical Priorities Advisory Group committee papers can be accessed here.

What we have decided

NHS England has carefully reviewed the evidence to treat patients with moderate haemophilia A without factor VIII (FVIII) inhibitors with emicizumab as prophylaxis. We have concluded that there is enough evidence to make the treatment available at this time.

The evidence review which informs this commissioning position can be accessed here.

Links and updates to other policies

This document is linked to the following policy:

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

'Emicizumab as prophylaxis in people with severe congenital haemophilia A without factor VIII inhibitors (all ages)'

Plain language summary

About Haemophilia A

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) (FVIII) in their blood, or it isn't working properly. This means they cannot form strong clots and so they bleed for longer than usual.

Haemophilia A can be categorised from mild to severe, depending on the level of clotting FVIII activity. Mild deficiency is categorised as 5–40% FVIII activity, moderate deficiency as 1 to 5% FVIII activity and severe deficiency as <1% FVIII activity (Doncel et al., 2023). 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 episodes into joints initially causes pain, bruising and swelling. Over time this leads to irreversible joint damage, reducing the person's ability to move and reducing their quality of life. Bleeding into other areas of the body, such as the brain, may be fatal.

Some patients with moderate haemophilia A are described as having a 'severe bleeding phenotype'. This is a term used in clinical practice with no one single definition, but generally in adults the term refers to those with ongoing bleeding events or joint damage or requiring FVIII prophylaxis. In children, the aim is to identify this group before bleeding episodes and joint damage occurs, so the clinical consensus is that a severe bleeding phenotype refers to those with baseline FVIII levels of 1–3 IU/dL in this age group.

People with moderate haemophilia A are currently treated by replacing the missing FVIII. FVIII replacement treatment prevents bleeds and therefore reduces subsequent damage to joints. However, approximately one third of people who receive FVIII replacement therapy will develop FVIII inhibitors which make the replacement FVIII ineffective.

This policy relates to people with moderate haemophilia A without FVIII inhibitors.

About current treatment

There is currently no cure for haemophilia A and 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 FVIII into the vein (either directly or via a central venous access device for patients who require it), given every 2 to 3 days. If a bleed occurs, it is treated with injections of FVIII.

About the new treatment

Emicizumab is a drug used to prevent bleeding or reduce the number of bleeds in people with haemophilia A. It is administered as an injection that goes under the skin. Emicizumab works by binding to FX and activated FIX which brings those clotting factors near each other and activates the blood clotting system even if no FVIII is present. This is different to how replacement FVIII works. When a person starts on emicizumab they need to inject it once a week for the first 4 weeks (this is called a loading dose). After this, the person can inject emicizumab either once a week, once every 2 weeks or once every 4 weeks The

dose given depends on the patient's weight. Emicizumab is licensed for routine prophylaxis of bleeding episodes in patients with haemophilia A (congenital FVIII deficiency) with FVIII inhibitors, or without FVIII inhibitors who have severe disease (FVIII < 1%) or moderate disease (FVIII >1% and <5%) with severe bleeding phenotype.

Epidemiology and needs assessment

According to the International Society on Thrombosis and Haemostasis (ISTH), moderate haemophilia A is defined as having FVIII levels between 1 and 5% of normal levels. Prophylaxis is indicated in people with moderate haemophilia A with a clinically severe phenotype. In adults, this includes those with joint damage and any joint bleeds in a year, or more than 3 to 4 bleeds in a year, or currently on prophylaxis with FVIII for more than 12 weeks, and for all children those with baseline FVIII levels of 1–3 IU/dL.

The exact number of moderate haemophilia A with a severe phenotype is unknown. Most people with moderate severity haemophilia A (baseline FVIII level of 1-2 IU/dL) will have a severe bleeding phenotype, but not all. Few people with a baseline FVIII level >2 IU/dL will have a severe phenotype. Given this, the number of people with haemophilia A 1-3% registered with the UK National Haemophilia Database (NHD) between April 2022 and March 2023 was 487, with the estimated population in England being 385. About a quarter to a third of these patients required prophylaxis, so an estimated 80 more patients are likely to be eligible for prophylactic treatment under this policy.

Implementation

NHS England will routinely commission emicizumab as prophylaxis for patients meeting all of the following inclusion criteria, and none of the exclusion criteria.

Inclusion criteria

Patients who meet **ALL** of the following inclusion criteria will be eligible for prophylactic treatment with emicizumab:

- A confirmed diagnosis of moderate haemophilia A (defined as FVIII levels ≥ 1% and ≤ 5%

AND

- A severe phenotype, fulfilling ONE of the following criteria:
    - joint damage or any joint bleeds in a year

    OR

    - more than 3 treated bleeds in 12 months

    OR

    - currently receiving prophylaxis with FVIII for more than 12 weeks

    OR

    - children with baseline factor levels of 1–3 IU/dL

Exclusion criteria

Patients who meet ANY of the following criteria are not eligible for prophylactic treatment with emicizumab under this policy:

- a FVIII inhibitor confirmed on more than one occasion by a Nijmegen-modified Bethesda assay (this would be covered by policy 'Emicizumab as prophylaxis in people with congenital haemophilia A with factor VIII inhibitors (all ages)').
- Individuals with contraindications to emicizumab as outlined in the summary of product characteristics (SmPC).

Starting criteria

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. In common with any prophylaxis regimen in the management of haemophilia A, patients on emicizumab are also at risk of traumatic bleeds and will continue to possess a small quantity of FVIII at home for the self-management of bleeds.

As with current practice, patients, or their carers, will be counselled routinely on the recognition and management of bleeds and the need for clinical advice. 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, such as Haemtrack™.

Stopping criteria

Treatment with emicizumab should be withdrawn and stopped immediately in the case of a severe allergic reaction.

After 6 to 12 months treatment with emicizumab, it should be withdrawn and stopped in the following situations:

- Where there is an annualised bleeding rate of 5 or more spontaneous bleeds or bleeds related to activities of daily living compared with the patient's baseline bleeding rate over the 12 months preceding emicizumab when treated with intravenous FVIII.
- For patients who are treatment naïve, where there is an annualised bleeding rate of 5 or more spontaneous bleeds or bleeds related to activities of daily living.
- Loss of efficacy due to the development of antibodies to emicizumab, or as otherwise clinically determined.

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

- An occurrence of a thrombotic event or other significant adverse reaction or any major comorbidity arises or is identified during treatment.
- Neutralising antibodies to emicizumab are identified.

Dosing

Dosing will be consistent with the license and the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) dosing algorithm, which all prescribers will comply with. The algorithm is designed to:

- Minimise the volume which patients will be required to inject.
- Minimise the risk of dosing errors.
- Minimise drug waste from each vial, so that when selecting the maintenance dose regimen for each patient the frequency may be adjusted to weekly, every 2 weeks or every 4 weeks. Doses will be determined by the patient's weight as per the licensed indications.

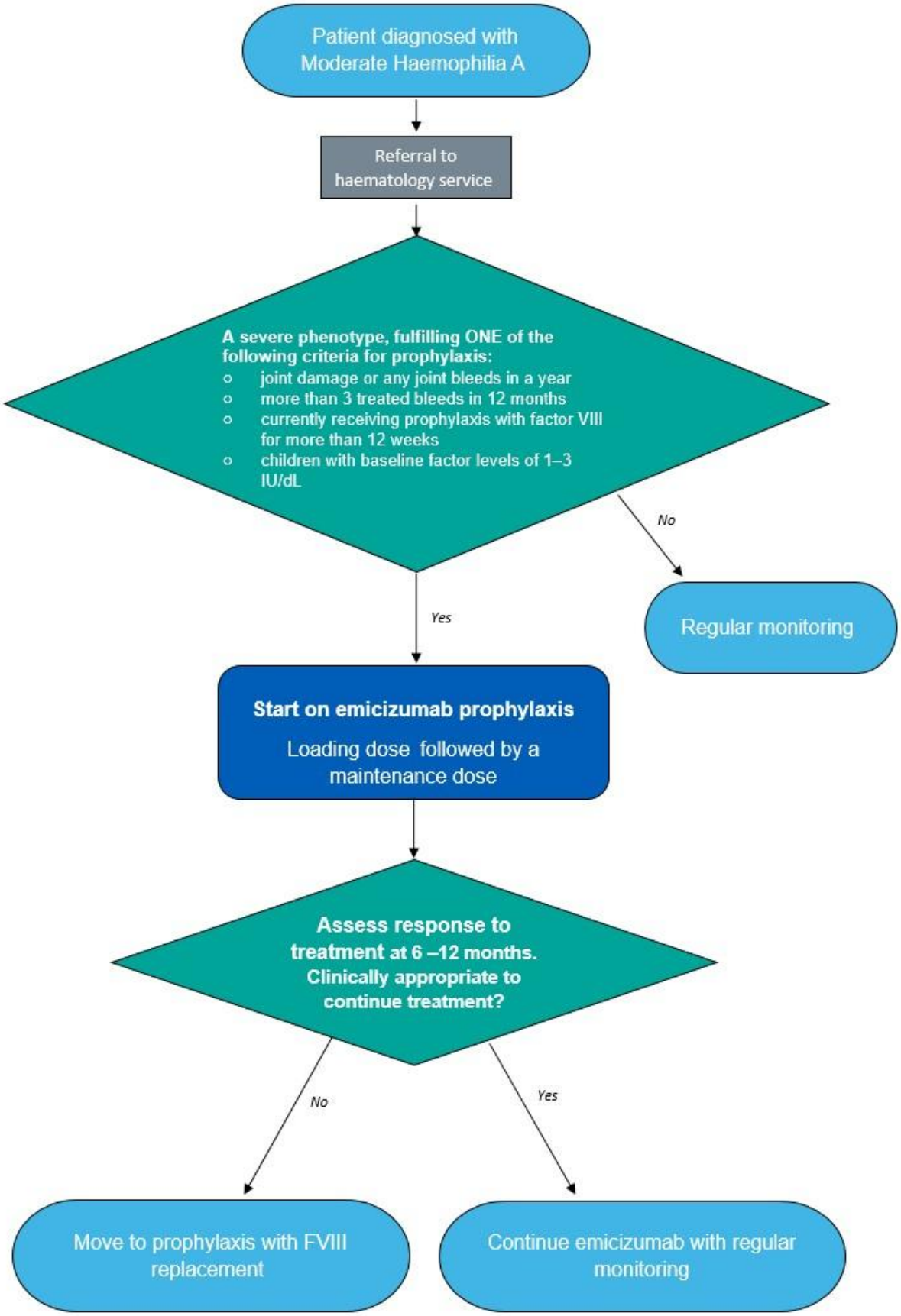
The use of emicizumab as prophylaxis in moderate haemophilia A without inhibitors and with a severe bleeding phenotype is a licenced indication.

Monitoring

The following monitoring should be undertaken:

- Patients on long term prophylaxis should have their regimens reviewed at least every 6 months.
- Patients should have their FVIII inhibitor levels tested every 12 months by an appropriate technique that enables the detection of inhibitors even in the presence of emicizumab. Testing may be more frequent in paediatric patients.
- If a patient using emicizumab prophylaxis requires FVIII treatment for a bleed, they must be monitored regularly for inhibitors after the use of FVIII if they have had less than 50 exposure days to FVIII.
- 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)

Patient pathway



Governance arrangements

This policy should be used in conjunction with the following Service Specialised Specification for Haemophilia (all ages) B05/S/a.

Provider organisations must register all patients using prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

Mechanism for funding

Emicizumab is categorised as a high-cost drug to be reimbursed under the cost and volume process.

Audit requirements

All patients must be registered with the UK National Haemophilia Database. 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 an ongoing national audit which will include:

- Starting dose and dose changes to review compliance with protocols.
- Cardiovascular risk factors and history when commencing emicizumab.
- FVIII usage.
- Number of bleeding episodes per year (and annualised baseline number of bleeding episodes before commencing emicizumab prophylaxis).
- Haemophilia Joint Health Score (HJHS).
- Adverse reactions (including thrombotic events and allergic reactions).
- Results from testing for FVIII inhibitors for all patients.

In addition, data will be collected from NHS England's Prior Approval Request forms which will inform commissioners about prior treatment modalities and other important baseline treatment parameters.

Policy review date

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

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 review 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.

Definitions

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.
Bethesda units	The Bethesda assay is used to quantify the concentration of FVIII inhibitor. One Bethesda unit (BU) is the amount of inhibitor required to neutralise 50% of a unit of FVIII in normal plasma after incubation at 37°C for 2 hours.
Central venous access device	A catheter that is inserted into the central venous system with the internal tip sitting within the superior/inferior vena cava or right atrium. This allows the administration of fluids, blood products, medication and other therapies into the bloodstream.
Factor VIII (FVIII)	A protein involved in blood clotting.
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 FVIII, an essential blood-clotting protein.
Inhibitor	An antibody produced by the immune system which neutralises and deactivates FVIII.

References

Sarmiento Doncel, S., Díaz Mosquera, G. A., Cortes, J. M., Agudelo Rico, C., Meza Cadavid, F. J., & Peláez, R. G. (2023). Haemophilia A: A Review of Clinical Manifestations, Treatment, Mutations, and the Development of Inhibitors. Hematology reports, 15(1), 130–150. https://doi.org/10.3390/hematolrep15010014

References which inform this Clinical Policy are located within evidence summary:

Négrier et al. (2023) Emicizumab in people with moderate or mild haemophilia A (HAVEN 6): a multicentre, open-label, single-arm, phase 3 study. Lancet Haematology. 10 (3): e168-e177. doi: 10.1016/S2352-3026 (22)00377-5