AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

Evidence summary report for a limited assessment

Emicizumab (Hemlibra®) 30 mg/ml and 150 mg/ml solution for subcutaneous injection

Indication under consideration
The routine prophylaxis of bleeding episodes in patients with haemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors who have moderate disease (FVIII ≥ 1% and ≤ 5%) with severe bleeding phenotype.

Company
Roche Products Ltd

Background
Haemophilia A (HA) is a rare genetic condition, usually in males, that affects the blood's ability to clot due to missing or defective clotting factor protein called factor VIII (FVIII). 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 1–5% FVIII activity and severe deficiency as <1% FVIII activity (Doncel et al., 2023). HA causes prolonged external bleeding after trauma, and internal bleeding, for example into joints or the brain, either as a result of a trigger event such as a fall or impact or spontaneously without an obvious trigger event (Great Ormond Street Hospital). Bleeding episodes into joints initially cause pain, swelling and restriction of movement, which require repeated intravenous injections to resolve. Any joint bleed can cause long term joint damage which over time leads to irreversible joint damage, reducing mobility and quality of life. Bleeding into other areas of the body, such as the brain, may be fatal (NHS England).

Prophylaxis treatment for HA decreases the frequency of bleeding, preventing or minimising joint damage or slowing down progression of established joint disease (ISTH). The expected outcome of optimised prophylaxis is that a child started on prophylaxis before the second joint bleed or the age of 3 years, in the absence of documented joint disease, will reach adulthood with normal joints and live a full and active life, in the absence of bleeds. If started later and depending on the degree of established joint disease, prophylaxis will maximise function long-term, slow disease progression, reduce pain and maintain quality of life (Rayment et al 2020).

According to the International Society on Thrombosis and Haemostasis (ISTH), prophylaxis is indicated in people with moderate HA without inhibitors and with a severe bleeding phenotype (ISTH). There is no single one definition for the term 'severe bleeding phenotype' but according to NHS England this includes adults 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 all children with baseline FVIII levels of 1–3 IU/dL (NHS England).
People with moderate HA are currently treated with prophylaxis FVIII replacement treatment. However, approximately one third of people who receive FVIII replacement therapy will develop FVIII inhibitors which make the replacement FVIII

ineffective (NHS England). Clinical expert opinion from the Cardiff Haematology Centre also states that some adults with moderate HA with severe bleeding phenotype decline FVIII prophylaxis and receive treatment with FVIII on-demand only (i.e. in the presence of bleeding or following trauma).

Emicizumab is an alternative prophylaxis treatment for haemophilia A and can be used in all age groups. Although guidance advises starting prophylaxis prior to age 3 to maximise outcomes, clinical practice in Wales and the UK is to start prophylaxis with emicizumab as early as possible and within the first month of life. It is licensed for the routine prophylaxis of bleeding episodes in patients with haemophilia A with FVIII inhibitors and for people without FVIII inhibitors who have either severe HA (FVIII < 1%) or who have moderate HA (FVIII ≥ 1% and ≤ 5%) with a severe bleeding phenotype. Patients in both Wales and England with HA with FVIII inhibitors or without inhibitors but with severe disease already have routine access to emicizumab prophylaxis through commissioning by the NHS Wales Joint Commissioning Committee (NWJCC) and NHS England respectively.

This assessment considers the remaining subpopulation of the indication i.e. people with moderate HA without FVIII inhibitors and with a severe bleeding phenotype for which no all-Wales guidance is available. Routine access to emicizumab for this sub population has recently been enabled in England (NHS England).

Guidance and recommendations

The International Society on Thrombosis and Haemostasis (ISTH) clinical practice guideline for treatment of congenital haemophilia A and B based on the Grading of Recommendations Assessment, Development, and Evaluation methodology strongly recommends that individuals with severe and moderately severe (i.e. with a severe bleeding phenotype even if FVIII plasma levels are ≥2 IU/dL) HA without inhibitors are given prophylaxis over episodic treatment of bleeding events. It conditionally recommends that either prophylaxis with emicizumab or prophylaxis with FVIII concentrate should be given to these individuals and acknowledges that emicizumab may offer a lower treatment burden for patients given its weekly, biweekly, or every 4-week schedule and subcutaneous administration. The World Federation of Haemophilia (WFH) guidelines also strongly recommend prophylaxis for patients with HA with a severe phenotype without inhibitors (which includes patients with moderate HA with a severe phenotype). The WFH guidelines state that emicizumab should allow for less burdensome prophylaxis, which might improve adherence and might lead to increased uptake of prophylaxis among patients not currently on prophylaxis (including those with moderate haemophilia), permitting them increased participation in social and sports activities.

In July 2025, the NHS England clinical commissioning policy Emicizumab for prophylaxis of bleeding episodes in people with moderate haemophilia A without inhibitors (all ages) enabled routine access to emicizumab for the indication being considered by this assessment.

The company confirm that emicizumab for the indication under consideration has been offered to Wales at the same discounted price as NHS England. This

commercial access arrangement (CAA) has been reviewed by the Medicines Value Unit and confirmed as implementable in NHS Wales.

Technology

Emicizumab works by acting as a bispecific antibody that bridges activated factor IX (FIXa) and factor X (FX) in the blood, mimicking the missing function of activated factor VIII in patients with HA. By bringing these two coagulation factors together, emicizumab facilitates the coagulation cascade, thereby restoring effective blood clotting and preventing or reducing bleeding episodes. Emicizumab has no structural relationship or sequence homology to FVIII and, as such, does not induce or enhance the development of direct inhibitors to FVIII (SmPC, Parisi et al, 2023).

Emicizumab is indicated for routine prophylaxis of bleeding episodes in patients of all ages with haemophilia A (congenital factor VIII deficiency):

- with factor VIII inhibitors
- without factor VIII inhibitors who have:
    - severe disease (FVIII < 1%)
    - moderate disease (FVIII ≥ 1% and ≤ 5%) with severe bleeding phenotype.

Administration of emicizumab is by subcutaneous injection. The recommended dose for all patient populations is 3 mg/kg once weekly for the first 4 weeks (loading dose), followed by a maintenance dose from week 5, of either 1.5 mg/kg once weekly, 3 mg/kg every two weeks, or 6 mg/kg every four weeks. The loading dose regimen is the same, irrespective of the maintenance dose regimen. The maintenance dose regimen is selected based on clinician and patient/caregiver dosing regimen preference to support adherence.

Emicizumab is intended for use under the guidance of a healthcare professional. After proper training in subcutaneous injection technique, a patient may self-inject emicizumab, or the patient's caregiver may administer it, if their healthcare professional determines that it is appropriate (SmPC).

Marketing authorisation date: 24 May 2023 for the indication under consideration.

Criteria for limited assessment

The Scrutiny panel reviewed the company request for the assessment of emicizumab and considered that it was suitable for a limited assessment via the Licensed One Wales Medicines Assessment Group (LOWMAG). They cited the following reasons for this decision:

- Its use is recommended as a prophylactic option for moderate haemophilia A in international guidelines.
- The anticipated budget impact is expected to be low.
- It is available to this patient population in England.

The AWMSG Scrutiny Panel agreed that as the case for clinical effectiveness is established it does not warrant further review. Therefore, the limited assessment should give an overview of current use, equity of access and budget impact only.

Comparator(s) and place in pathway

People in Wales with moderate HA with a clinically severe phenotype are currently offered prophylaxis with recombinant factor VIII (rFVIII) delivered by intravenous injection. The company submission suggests that there are two comparators relevant for this assessment; standard half-life (SHL) rFVIII and extended half-life (EHL) rFVIII. However, clinicians in Wales advise two EHL rFVIII products are used for prophylaxis in this group of patients; older children and adults receive Esperoct® whilst children under 12 years of age are generally given Elocta®. These involve intravenous treatment 2 to 4 times a week which can be administered at home by the patient or the patient's caregiver after suitable training (The Haemophilia Society). Insertion of a port-a-cath may be necessary for younger children or those whose veins are difficult to access. Clinical experts advise that, for children, this requires insertion under general anaesthetic and seven days hospital admission; this can only be performed once a child reaches 10 kg in weight (around 1 year of age). The use of a port-a-cath is also associated with an ongoing risk of severe infection whilst the device is in situ (Ljung, 2007).

Clinicians in Wales state that prophylaxis is discussed with all patients with moderate HA and emicizumab will offer an alternative option to EHL rFVIII prophylaxis for suitable patients meeting specific starting criteria. Patients who would benefit from prophylaxis but are not able to manage the treatment burden of intravenous rFVIII treatment every 2-3 days are most likely to benefit from this therapy, as well as families with multiple affected children. In babies, the risk of joint bleeds increases once mobilisation starts (which can be from 6 months of age) which is prior to the age when a port-a-cath can be inserted to aid administration of rFVIII prophylaxis. The easier administration of emicizumab prophylaxis (which can be given from birth) by subcutaneous injection every 14 days compared to intravenous rFVIII treatment 2-3 times a week will also benefit this age group and their families.

Budget impact

The company estimates for the budget impact is given in Table 1. Emicizumab is costed at the discounted price agreed between the company and NHS Wales for this indication of [commercial in confidence information removed]. The company comparators used are a standard half-life (SHL) rFVIII product costed at £0.07 per unit (IU/mg) and an extended half-life (EHL) rFVIII product costed at £0.15 per unit (IU/mg); it is assumed that most patients will be on EHL rFVIII and hence, the comparator predominantly displaced by emicizumab.

Patient number estimates provided by the applicant company are based on UK registry data submitted to NHS England and extrapolated for Wales using published population data. The exact number of people with moderate haemophilia A with a severe bleeding phenotype is unknown; estimates are based on the assumption that most people with moderate severity haemophilia A (baseline FVIII level of 1-2 IU/dL) will have a severe bleeding phenotype but few people with a baseline FVIII level >2 IU/dL will. Therefore, eligible patient numbers are based on the number of people

with HA with FVIII activity of 1-3% registered with the UK National Haemophilia Database (NHD) between April 2022 and March 2023 which was 487; this was also the figure used by NHS England in the development of their commissioning policy. Based on population estimates, Wales is assumed to account for 5% (24) of these cases. The applicant company state that there are various estimates of the proportion of such patients that require prophylaxis, ranging from a quarter to a half. Therefore, they suggest an estimated 6-12 patients may be eligible for this indication in Wales with the expectation being towards the upper end of this estimate, and between 8-10 patients prescribed emicizumab.

Dosing of both emicizumab and rFVIII prophylaxis is weight based. The company has based all their calculations on the cost of treating an adult male of average weight (85 kg), however, no details have been given on the dosing and the frequency of the dosing used to calculate the comparator rFVIII treatment costs. Costs for emicizumab are based on the maintenance phase of therapy for all patients.

Table 1. Company model: budget impact estimate for emicizumab in NHS Wales

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients	**22**	**23**	**24**	**25**	**26**
Number of patients predicted to take-up prophylaxis	11	11	12	12	13
Uptake of new medicine (%)	60%	80%	80%	80%	80%
Number of patients receiving new medicine allowing for discontinuations	7	9	10	10	10
Medicine acquisition costs in a market without new medicine	£868,227	£936,495	£1,007,259	£1,080,521	£1,156,281
Medicines acquisition costs in a market with new medicine	¶¶	¶¶	¶¶	¶¶	¶¶
Net medicine acquisition costs	¶¶	¶¶	¶¶	¶¶	¶¶

¶¶: commercial in confidence figure removed

Critique of company BI model

- AWTTC agree with the predicted number of patients who will be treated with emicizumab for this indication; clinical experts from the Haematology Centre at Cardiff and Vale UHB estimates that 20 patients (which includes those on recombinant FVIII prophylaxis and those who have declined FVIII prophylaxis and are treated on-demand) would be eligible for this treatment within the

Bleeding Disorders Network Wales with a predicted 50% uptake of emicizumab.

- The budget impact considerations are limited to acquisition costs only; other resource use is not included (e.g. monitoring costs and costs associated with adverse events). As both treatments are generally self-administered at home, any additional resource costs (such as initiation of treatment in a healthcare setting and homecare delivery costs etc) are assumed to be similar and so have not been accounted for. Monitoring and adverse event costs have been excluded although they are expected to be broadly similar for all prophylaxis options.
- The company BI model uses both standard half-life (SHL) rFVIII and extended half-life (EHL) rFVIII as comparators. However, clinicians in Wales advise SHL is not used in this population and two EHL rFVIII products are used depending on patient age. Comparator costs have been estimated by the company based on field intelligence; however, the [commercial in confidence information removed] than that used in the BI model. Therefore, the cost-savings predicted by the company in switching patients to emicizumab may not be realised.
- No details on the dosing and the frequency of dosing used to calculate comparator rFVIII products have been given. Clinicians advise that this can be variable between patients with dosing between 30 – 50 IU/kg with a frequency ranging from every other day to twice weekly. This will impact on the net acquisition costs predicted.
- For simplicity, the company BI model assumes that all patients are adults of 85 kg in weight although emicizumab is licensed for all ages and it is reasonable to expect that a proportion of patients will be children. Additionally, the EHL rFVIII product commonly used for prophylaxis for children aged 12 years and under in this patient population is [commercial in confidence information removed] than the one used for older children and adults. Therefore, the actual budget impact may be significantly affected by the proportion of younger children to adults receiving emicizumab for this indication.

To take into account the critique points raised above, Table 2 gives simplified AWTTC-calculated costs per year for an 85 kg adult and a 23 kg child (approximately 7 years old). For simplicity, emicizumab costs are based on a maintenance cycle of 3 mg/kg every 2 weeks although it should be noted that emicizumab costs for the first year of treatment will be higher to account for the two extra doses required during the initiation phase. Costs for the two rFVIII comparators are given for the minimum and maximum dose and dosing frequency as advised by clinical experts from the Cardiff Haematology Centre.

Table 2. Costs associated with use of emicizumab per year per patient in Wales in comparison to rFVIII products

	Annual cost
Emicizumab acquisition cost for an 85 kg adult	¶¶
Emicizumab acquisition cost for a 7 year old (23 kg) child	¶¶
Comparator (Esperoct®) acquisition costs for an 85 kg adult*	
Minimum	¶¶
Maximum	¶¶
Comparator (Elocta®) acquisition costs for a 23 kg child**	
Minimum	¶¶
Maximum	¶¶
Net acquisition cost range of emicizumab compared to rFVIII for a 85 kg adult	¶¶
Net acquisition cost range of emicizumab compared to rFVIII for a 23 kg child	¶¶

* Minimum based on a dose of 30 IU/kg twice a week, maximum based on a dose of 50 IU/kg every 3 days
** Minimum based on a dose of 30 IU/kg every other day, maximum based on a dose of 50 IU/kg every other day.
All costs exclude VAT. Some vial wastage assumed.
¶¶: commercial in confidence figure removed

[commercial in confidence information removed]

It is difficult to estimate with any certainty an overall budget impact for the predicted 10 patients that may receive this treatment for moderate HA in Wales as costs are weight-dependent and so will vary between different individuals, and budget impact will be substantially impacted by the proportion of children to adults contributing to this overall number, and hence the rFVIII comparator product displaced. AWTTC has included three scenarios below which give an indication on how the budget impact may be affected taking these factors into account.

Table 3. Scenario budget impact estimates for emicizumab in Wales

Scenario	Annual cost
Scenario 1: 100% of patients are adults of 85 kg with full displacement of rFVIII Esperoct® (dose 40 IU/kg twice weekly)	
Emicizumab* acquisition cost for 10 adults	¶¶
rFVIII acquisition costs for 10 adults	¶¶
Net acquisition cost of emicizumab	¶¶
Scenario 2: 80% of patients are adults of 85 kg with full displacement of rFVIII Esperoct® (dose 40 IU/kg twice weekly), 20% of patient are children of 23 kg with full displacement of rFVIII Elocta® (dose 40 IU/kg every other day)	
Emicizumab* acquisition cost for 8 adults and 2 children	¶¶
rFVIII acquisition costs for 8 adults and 2 children	¶¶
Net acquisition cost of emicizumab	¶¶
Scenario 3: 50% of patients are adults of 85 kg with full displacement of rFVIII Esperoct® (dose 40 IU/kg twice weekly), 50% of patient are children of 23 kg with full displacement of rFVIII Elocta® (dose 40 IU/kg every other day)	
Emicizumab* acquisition cost for 5 adults and 5 children	¶¶
rFVIII acquisition costs for 5 adults and 5 children	¶¶
Net acquisition cost of emicizumab	¶¶
* Based on a maintenance cycle of 3 mg/kg every 2 weeks All costs exclude VAT. Some vial wastage assumed. ¶¶: commercial in confidence figure removed	

In the calculations above, it is assumed that all patients receiving emicizumab have been switched from rFVIII prophylaxis which may not be the case. However, the acquisition cost of emicizumab may be offset to some extent by the costs of any on demand rFVIII treatments required by patients who previously opted out of receiving rFVIII prophylaxis but have chosen to receive emicizumab prophylaxis.

[Confidential information removed].

Impact on health and social care services

No additional burden on health or social care services is expected. No additional monitoring is required for emicizumab prophylaxis over prophylaxis with rFVIII. It may be expected that there may be a greater uptake of prophylaxis with emicizumab than with current rFVIII products due to the reduced treatment burden, resulting in reduced frequency of bleeding events and hence lower burden on the healthcare system.

Patient factors

The submission from Haemophilia Wales highlights the impact haemophilia has on not only people with the condition but also their families and caregivers and that their lives are structured around managing it. Moderate haemophilia can cause difficulties with education and work prospects due to time needed to manage and recover from bleeds and can have an enormous impact on both physical and mental health.

Ongoing bleeds can often cause long term joint and muscle damage necessitating further interventions and joint replacements. Prophylaxis with intravenous rFVIII can present challenges, including difficulties in preparing injections, obtaining venous access in babies and children, particularly those with chubby limbs, and in older adults with damaged veins due to historical interventions and frailty, as well as the extensive training required from clinicians for home administration. Haemophilia Wales report positive experiences of people receiving emicizumab with many stating that it has been life-changing, providing them with a freedom they had not previously experienced. Parents of affected children express that stress levels are lessened as emicizumab removes the constant worry of unexpected bleeding. Haemophilia Wales highlighted prophylaxis with subcutaneous emicizumab has a substantially lower treatment burden for patients and their families than intravenous rFVIII due to both the method of dosing and the longer time intervals between doses.

Unlike for rFVIII prophylaxis in some young children, a port-a-cath for emicizumab dose delivery is not required, and effective prophylaxis may be easier to give to infants too young for port-a-cath insertion. Clinical experts also highlight that an increase in bruising is noted when infants start to mobilise if prophylaxis is not given, which can lead to non-accidental investigations/safeguarding concerns being raised which can be stigmatising to parents. Being able to start prophylaxis from birth with subcutaneous therapy will offer particular benefit to this patient group.

Equality impact assessment

AWTTC have completed an Equality and Health Impact Assessment in parallel with each development stage of the project. This follows the five ways of working for public bodies, and work to achieving the wellbeing goals, outlined in the Well-Being of Future Generations (Wales) Act 2015.

It is not expected that emicizumab will have a potential negative impact on people based on the protected characteristics of the Equality Act 2010. However, due to the genetics of haemophilia A, we may expect a positive impact for males who are much more likely to have this condition and thus require treatment.

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