NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Clinical evidence review for emicizumab for routine prophylaxis of bleeding episodes in patients with severe haemophilia A without factor VIII inhibitors

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Prepared by: NICE on behalf of NHS England Specialised Commissioning

About this clinical evidence review

Clinical evidence reviews are a summary of the best available evidence for a single technology within a licensed indication, for commissioning by NHS England. The clinical evidence review supports NHS England in producing clinical policies but is **not NICE guidance or advice**.

Summary

This evidence review considers emicizumab for the routine prophylaxis of bleeding episodes in people with severe haemophilia A without factor VIII inhibitors. The evidence review was undertaken in line with NHS England's methods for undertaking clinical evidence reviews.

A literature search was done, which identified 90 references (see appendix 1 for search strategy). The company also provided a submission of evidence. One published study was included in this review.

Evidence of the effect of emicizumab comes from one 24-week open-label, randomised controlled trial including a total of 152 participants (89 randomised and 63 non-randomised; Mahlangu et al. 2018). The key efficacy results for the study were only reported for the 89 randomised participants. Participants in the study had a confirmed diagnosis of severe congenital haemophilia A without factor VIII inhibitors and were receiving episodic (on-demand) or prophylactic treatment with factor VIII.

Effectiveness

Evidence from the 24-week randomised controlled trial suggests that in people who had previously received episodic treatment with factor VIII, emicizumab 1.5 mg/kg weekly (n=36) and emicizumab 3.0 mg/kg every 2 weeks (n=35) were associated with a significant reduction in bleeds requiring treatment compared with no prophylaxis (n=18; annualised rate of 1.5 and 1.3 events respectively versus 38.2 events, risk ratio [RR] 0.04 and 0.03, both $p<0.001$). This outcome suggests that people with haemophilia A without factor VIII inhibitors who are treated with emicizumab can expect to have fewer bleeds each year that require treatment, than if they did not were not treated with emicizumab.

Evidence from the same trial suggests that people receiving emicizumab prophylaxis did not have statistically significant improvements in their quality of life compared with people receiving no prophylaxis.

A sub-group of non-randomised participants who had been involved in a real-world, non-interventional cohort study (n=48) had a significantly lower treated annualised bleeding rate on emicizumab prophylaxis (1.5 events) compared with factor VIII prophylaxis (4.8 events; RR 0.32, 95% 0.20 to 0.51, p<0.001). However, such intra-individual comparisons should be interpreted with caution, particularly when comparing results of real-world observational studies with the results of more rigidly controlled clinical trials. The results of this study suggest that emicizumab may be as least as effective as real-world factor VIII prophylaxis. However, it must be acknowledged that emicizumab has not been directly compared with factor VIII replacement treatment.

Safety and tolerability

Adverse events were common, reported in 85% of participants receiving emicizumab prophylaxis. The most common were injection-site reaction, arthralgia (joint pain) and nasopharyngitis.

One person discontinued treatment with emicizumab due to a number of adverse events that were considered to be related to emicizumab.

There were no deaths, no cases of thrombotic microangiopathy and no thrombotic events. There were no serious adverse events related to co-exposure to emicizumab and factor VIII. No new factor VIII inhibitors developed in participants receiving emicizumab, although 1 person who had previously undergone immune tolerance induction had re-emergence of a detectable inhibitors. No participants developed antibodies to emicizumab during the study by Mahlangu et al. (2018). The SPC for emicizumab states that 4 participants (2.1%) in the phase I/II clinical trials tested positive for anti-emicizumab antibodies, all of which were non-neutralising.

Evidence gaps and limitations

Emicizumab prophylaxis has not been directly compared with current gold standard treatment, which is individually tailored factor VIII prophylaxis, in a pair-wise comparison randomised controlled trial.

The primary efficacy endpoint of the Mahlangu et al. (2018) study was reported over at least 24 weeks (median duration of treatment approximately 30 weeks), data beyond this time-point had not been published at the time of the review.

The efficacy and safety of emicizumab prophylaxis in children with severe congenital haemophilia A without inhibitors aged less than 12 years has not been published at the time of this review, although emicizumab is licensed in all age groups.

Table of contents

Abbreviations

Term	Definition
dL	Decilitre
Haem-A-QoL	Haemophilia Quality of Life Questionnaire
ITI	Immune Tolerance Induction
IU	International unit

Medical definitions

Term	Definition
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 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	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	A protein involved in blood clotting
Haemophilia A	An inherited condition, affecting predominately males, in which there is excessive bleeding following trauma or spontaneously due to insufficient production of factor VIII, an essential blood-clotting protein
Inhibitor	An antibody produced by the immune system which neutralises and deactivates factor VIII
Inhibitor titres	Measured in Bethesda units (BU). The higher the number of Bethesda units, the more inhibitors are present.
Target joint	A joint in the body where there are recurrent bleeds
Titre	The concentration of a substance (such as an antibody) in solution, which is worked out by a method called titration

1 Introduction

Disease background

1.1 Haemophilia is an inherited genetic condition of which there are 2 main types (haemophilia A and B). The most common is haemophilia A, a deficiency of coagulation factor VIII, which causes increased bleeding. It usually affects males, with a prevalence of between 1 in 5,000 and 1 in 10,000 in males. Recurrent bleeds lead to progressive joint damage and other complications (NHS England Clinical Commissioning Policy: Immune Tolerance Induction [ITI] for haemophilia A).

1.2 Standard treatment for haemophilia A is to replace the missing factor VIII, either through prophylactic intravenous infusions every 2 to 3 days to prevent bleeding episodes, or with on-demand (episodic) infusions to treat bleeding episodes when they occur.

1.3 Factor VIII can be given as 'standard' half-life' factor VIII (for example Advate and ReFacto AF) or as enhanced half-life factor VIII (for example Elocta).

Focus of review

1.4 In line with the anticipated extended marketing authorisation, the focus of this review is emicizumab for the routine prophylaxis of bleeding episodes in people with severe haemophilia A without factor VIII inhibitors.

Epidemiology and needs assessment

1.5 The UK national haemophilia database bleeding disorder statistics for April 2016 to March 2017 reports that there are 5,442 people in England with mild, moderate or severe forms of haemophilia A (not including low-level carriers; factor VIII level ≥40 IU/dL). Of these, 5,259 people do not have inhibitors to factor VIII,of whom 1,483 people have severe haemophilia.

1.6 The eligible patient population for emicizumab in the England is considered to be equivalent to the patients with severe haemophilia A without current inhibitors (n=1,483).

Table 1 Patient numbers

Estimates	Data source	Number of people
People with haemophilia A (excluding low-level carriers)	UK national haemophilia database bleeding disorder statistics for April 2016 to March 2017	**Total = 5,442** Severe = 1,625 Moderate = 703 Mild = 3,114
People with haemophilia A with current inhibitors		**Total = 182** Severe = 141 Moderate = 26 Mild = 15
People with haemophilia A without current inhibitors		**Total = 5,259** Severe = 1,483 Moderate = 677 Mild = 3,099
Definitions Severe = Factor VIII level <1 IU/dL, or <1% of normal Moderate = Factor VIII level 1 to 5 IU/dL, or 1-5% of normal Mild = Factor VIII level >5 to <40 IU/dL, or >5 to <40% of normal Low level carriers = Factor VIII level ≥40 IU/dL, or ≥40% of normal		

Product overview

Mode of action

1.7 Emicizumab is a bispecific monoclonal antibody designed to mimic factor VIII activity. Emicizumab bridges activated factor IX and factor X to restore the function of activated factor VIII, which is needed for effective haemostasis. Emicizumab has no structural relationship or sequence homology to factor VIII and, as such, does not induce or enhance the development of direct inhibitors to factor VIII (SPC for emicizumab). Emicizumab has a much longer half-life (26.7 days SPC for emicizumab) than factor VIII (19 hours, SPC for enhanced half-life factor VIII), meaning patients have more steady level of drug in their blood (fewer peaks and troughs in plasma concentration).

Regulatory status

1.8 Emicizumab does not currently have a marketing authorisation in the UK for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with haemophilia A without inhibitors. It has been studied in clinical trials in people with haemophilia A without inhibitors (Mahlangu et al. 2018).

1.9 At the time of this review emicizumab is licensed for routine prophylaxis of bleeding episodes in patients of all ages with haemophilia A with factor VIII inhibitors.

Dosing information

1.10 For people with haemophilia A and inhibitors to factor VIII the SPC for emicizumab states that the recommended dose for emicizumab is 3.0 mg/kg once weekly for the first 4 weeks (loading dose), followed by 1.5 mg/kg once weekly (maintenance dose). Emicizumab is administered as a subcutaneous injection.

1.11 Alternative maintenance doses were used in the clinical trials involving people with haemophilia A without inhibitors. In HAVEN 3 (Mahlangu et al. 2018) participants had either 1.5 mg/kg once weekly or 3.0 mg/kg every 2 weeks, and in HAVEN 4 (NCT03020160) participants received emicizumab 6 mg/kg every 4 weeks.

Treatment pathway and current practice

1.12 Once a diagnosis of haemophilia A is made, the severity of disease is determined by the factor VIII levels in the blood. Current treatment options are prophylactic or episodic treatment with factor VIII (either standard factor VIII or enhanced half-life factor VIII), the choice of which is guided by disease severity and bleeding history. In the UK, factor VIII prophylaxis is considered the gold standard care for people with severe haemophilia. People with moderate haemophilia A receive factor VIII prophylaxis or on-demand depending on their bleeding pattern. People with mild haemophilia who bleed frequently receive on-demand factor VIII

treatment. When spending extended periods of time away from home, patients must carry large volumes of factor VIII with them. Depending on the amount of factor VIII required to treat a patient, injections can range from twice daily to once every 2 to 3 days (see SPC for factor VIII).

2 Evidence

Literature search

2.1 A literature search was done, which identified 90 unique references (see appendix 1 for search strategy). These references were screened using their titles and abstracts and no full text references were obtained and assessed for relevance.

2.2 The company submission identified 4 references to published studies in their submission, and a reference to 1 study scheduled to be published before the end of August 2018 (after the search dates). Four of these studies were identified in the literature search and 1 was published after the literature was completed. As such 1 additional unique reference was identified.

2.3 Full text inclusion and exclusion criteria were applied to the identified study and this study was included in the clinical evidence review (see appendix 2 for inclusion criteria and a list of studies excluded at full text with reasons).

Overview of included studies

2.4 One open-label, phase III randomised controlled trial (RCT) identified by the company (published after the search dates) was included in this evidence review (Mahlangu et al. 2018; HAVEN 3). A summary of the characteristics of the included study is shown in table 2 (see evidence tables for full details).

Table 2 Summary of included studies

Study	Population	Intervention and comparison	Primary outcome
Mahlangu et al. 2018 (HAVEN 3 study) Open-label, phase III, randomised controlled trial	People aged 12 years and over with severe congenital haemophilia A without current factor VIII inhibitors, who were receiving episodic (on-demand) or prophylactic factor VIII infusions (89 randomised participants, 63 non-randomised participants, total n=152)	**Intervention:** emicizumab prophylaxis. All emicizumab groups had a loading dose of emicizumab 3.0 mg/kg once weekly for 4 weeks, followed by maintenance dose of either: • emicizumab 1.5 mg/kg once weekly (group A) • emicizumab 3.0 mg/kg every 2 weeks (group B) **Comparison:** no prophylaxis (group C) The study also included 63 people who had previously received prophylactic factor VIII, who were allocated in a non-randomised fashion to emicizumab 1.5 mg/kg once weekly (group D)	Rate of treated bleeding events (from baseline to at least 24 weeks). Reported as annualised bleeding rate.

Key outcomes

2.5 The key outcomes identified in the scope are discussed below for effectiveness and safety. Table 3 below provides a grade of evidence summary of key outcomes (see appendix 5 for the details of grading evidence). The more detailed evidence tables and results for each study are in appendices 3 and 4.

Study design

2.6 There were 4 treatment arms in the study by Mahlangu et al. (2018), 3 were randomised (groups A, B and C) and 1 non-randomised (group D). People who had previously received on-demand (episodic) factor VIII

were randomised to emicizumab 1.5 mg/kg once weekly (group A, n=36), emicizumab 3.0 mg/kg every 2 weeks (group B, n= 35) or no prophylaxis (group C, n= 18, control). The study also included 63 people who had previously received prophylactic factor VIII, who were allocated in a non-randomised fashion to emicizumab 1.5 mg/kg once weekly (group D), of whom 48 people had been involved in a non-interventional study (NCT02476942; Kruse-Jarres et al.,2019).

2.7 The primary outcome and most of the secondary outcomes of the study were based on comparisons between group A and C, and group B and C.

Effectiveness

Bleeding outcomes

2.8 The primary efficacy outcome in Mahlangu et al. (2018) was the difference in the rate of treated bleeding events over at least 24 weeks (median duration of treatment approximately 30 weeks) in people previously treated with on-demand factor VIII, reported as an annualised bleeding rate. Significantly lower annualised bleeding rates were seen in participants treated with emicizumab 1.5 mg/kg every week (group A; 1.5 events, 95% CI 0.9 to 2.5) and with emicizumab 3.0 mg/kg every 2 weeks (group B; 1.3 events, 95% CI 0.8 to 2.3) compared with no prophylaxis (group C; 38.2 events, 95% CI 22.9 to 63.8). The annualised bleeding rate was 96% lower in group A and 97% lower in group B, compared with no prophylaxis, $p<0.001$ for both comparisons.

2.9 Similar results were reported for all secondary bleeding outcomes in the trial, with both emicizumab groups having significantly lower annualised bleeding rates compared with no prophylaxis for: all bleeding events, spontaneous bleeding events, joint bleeding events and target-joint bleeding events (see appendix 4, table 6 for full results).

Health-related quality of life

2.10 Health-related quality of life was reported using the Haemophilia Quality of Life Questionnaire (Haem-A-QoL) physical health subscale score. The

Haem-A-QoL can assess health-related quality of life in people with haemophilia A and B, and consists of 46 items, composed of 10 subscales. 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 represents a clinically meaningful improvement in health-related quality of life (Wyrwich et al. 2015).

2.11 The adjusted mean difference in Haem-A-QoL physical health subscale score between group A and group C was 12.5 points (95% CI −2.0 to 27.0, p=0.09, not statistically significant). The adjusted mean difference between group B and group C was 16.0 points (95% CI 1.2 to 30.8, considered non-significant due to the order of the outcomes in the hierarchical testing framework).

2.12 There was no statistically significant difference in Haem-A-QoL physical health subscale score between either emicizumab group (group A or B) compared to the no prophylaxis group (group C).

Patient preference

2.13 Patient preference for treatment was an exploratory end point, assessed using the EmiPref patient survey. Emicizumab can be administered up to once every 4 weeks, which is considerably less frequent compared with factor VIII, which needs to be administered every 2 to 3 days. In addition to this, people have more flexibility to spend extended periods of time away from home without being required to carry large volumes of factor VIII. It would appear that this survey had been developed for this study but has not been externally validated.

2.14 In total, 95/134 participants (71%) completed the EmiPref survey, with 94% (95% CI 87 to 98) preferring emicizumab, and 45/46 participants in group D (98%, 95% CI 88 to 100) favouring emicizumab over factor VIII prophylaxis.

Intra-individual comparison

2.15 Mahlangu et al. (2018) reported intra-individual comparisons of emicizumab prophylaxis with factor VIII prophylaxis in a sub-set of participants previously recruited in a non-interventional cohort study (NCT02476942; Kruse-Jarres et al 2019). The non-interventional study collected real-world data on bleeding rates, health-related quality of life and safety in people being treated according to routine clinical practice.

2.16 The people in group D who had taken part in the non-interventional study (n=48) had a significantly lower annualised treated bleeding rate on emicizumab prophylaxis (1.5 events, 95% CI 1.0 to 2.3) compared with factor VIII prophylaxis (4.8 events, 95% CI 3.2 to 7.1), equating to a 68% reduction in bleeding rate (rate ratio [RR] 0.32, 95% 0.20 to 0.51, p<0.001).

2.17 While receiving factor VIII prophylaxis during the non-interventional study, 40% of participants had no bleeding events, compared with 54% of the same participants treated with emicizumab in the study by Mahlangu et al. (2018).

2.18 Results of such intra-individual comparisons should be interpreted with caution, particularly when comparing results of real-world observational studies with the results of more rigidly controlled clinical trials. Participants in the real-world, non-interventional study were treated according to local routine clinical practice, and as such there may have been important differences in how patients were managed between centres (Kruse-Jarres et al. 2019). Adherence to prophylactic factor VIII was variable in the non-interventional study, with around two-thirds of participants taking ≥80% of doses and one-third taking <80% of doses. Sub-optimal adherence to prophylactic factor VIII may account for the higher bleeding rate observed in the non-interventional study (Kruse-Jarres et al. 2019). It is also unclear how participants were selected from the real-world, non-interventional study, and selection bias may be present.

2.19 However, the authors of Mahlangu et al. (2018) state that intra-individual comparisons are appropriate because they control for person-related confounders; and such comparisons are particularly suitable for rare, stable diseases (such as haemophilia A) and for interventions without a carryover effect (factor VIII). They also state that the median annualised bleeding rate seen in the non-interventional study (1.8 events) was similar to that seen in prospective studies of prophylaxis with factor VIII (range 0.9 to 4.1 events).

2.20 The results of this study suggest that emicizumab may be as least as effective as real-world factor VIII prophylaxis. However, it must be acknowledged that emicizumab has not been directly compared with factor VIII replacement treatment.

Safety and tolerability

2.21 In total, 543 adverse events were reported in 127/150 participants (85%) who received emicizumab prophylaxis in the study by Mahlangu et al. (2018). The most common adverse events were injection-site reaction (reported in 25% of participants), arthralgia (joint pain; 19%) and nasopharyngitis (12%). Fourteen serious adverse events were reported, including bleeding events, a cardiac disorder and infections. No serious adverse events were considered by the investigators to be related to emicizumab treatment.

2.22 There were no deaths, no cases of thrombotic microangiopathy and no thrombotic events.

2.23 One person stopped treatment with emicizumab due to a number of adverse events (including insomnia, alopecia, nightmares, lethargy and headache) that were considered to be related to emicizumab.

2.24 In total, 215 events of co-exposure to emicizumab and factor VIII occurred in 64 participants, with 43 events involving an average dose of factor VIII of at least 50 IU/kg per day and 8 events lasting 24 hours or longer. There

were no serious adverse events related to co-exposure to emicizumab and factor VIII.

2.25 No new factor VIII inhibitors developed in participants receiving emicizumab. One participant had undergone immune tolerance induction (ITI) in 1987 and had a history of intermittent detectable inhibitors. This person had re-emergence of a detectable inhibitor at week 13 (1.6 Bethesda units, and this was still detectable at 0.7 Bethesda units at week 25.

2.26 No participants developed antibodies to emicizumab during the study by Mahlangu et al. (2018). The SPC for emicizumab states that 4 participants (2.1%) in the phase I/II clinical trials tested positive for anti-emicizumab antibodies, all of which were non-neutralising.

Evidence gaps and limitations

2.27 No RCTs were identified that directly compared emicizumab prophylaxis with standard treatment of factor VIII prophylaxis using a pair-wise comparison study design. The comparison of emicizumab with factor VIII prophylaxis is limited to intra-individual comparisons from a sub-group of participants (n= 48) previously involved in a real-world, non-interventional cohort study.

2.28 All participants involved in the Mahlangu et al. (2018) study (HAVEN 3) were aged 12 years and over; the median age was 38 years (range 13 to 77) and 8 participants (5.3%) were aged less than 18 years. The efficacy, safety and pharmacokinetics of emicizumab in children aged less than 12 years who have haemophilia A without inhibitors is not known.

2.29 There are a number of key differences between participants who had previously received episodic treatment with factor VIII (groups A, B and C) and those participants previously treated with prophylactic factor VIII (group D). Participants previously treated with prophylactic factor VIII were generally better controlled, having fewer bleeding events in the 24 weeks before the trial and having fewer target joints.

2.30 The primary efficacy outcome for Mahlangu et al. (2018) was reported over at least 24 weeks (median duration of treatment approximately 30 weeks). T); evidence for the effectiveness of emicizumab prophylaxis beyond this time-point in this patient group has not been published at the time of this review.

Table 3 Grade of evidence for key outcomes

Outcome measure	Study	Critical appraisal score	Applicability	Grade of evidence	Interpretation of evidence
Bleeding rate Reported using annualised rate of bleeding events treated with factor VIII Primary efficacy outcome	Mahlangu et al. 2018 (HAVEN 3)	7/10	Directly applicable	B	A 'treated' bleed is any bleeding event that required treatment with factor VIII. The investigators calculated the bleeding rate per day, and converted this to an annual bleeding rate. The study by Mahlangu and colleagues included 89 randomised participants who had previously received episodic treatment with factor VIII. People treated with emicizumab 1.5 mg/kg every week (n=36) or 3.0 mg/kg every 2 weeks (n=35) had an annual bleeding rate of 1.5 and 1.3 treated bleeds respectively, compared with 38.2 treated bleeds in the no prophylaxis group. These results suggest that people who were previously treated with episodic factor VIII who received emicizumab had a 96%-97% reduction in treated bleeds compared with people who received no prophylaxis. These results suggest that people who take emicizumab can expect to have substantially fewer bleeds each year that require treatment with factor VIII, compared with people who take no prophylaxis.
Health-related quality of life Reported used the Haemophilia Quality of Life Questionnaire (Haem-A-QoL) physical health subscale	Mahlangu et al. 2018 (HAVEN 3)	7/10	Directly applicable	B	The Haem-A-QoL is a tool for assessing quality of life in people with haemophilia. The questionnaire consists of 10 subscales, 1 of which is 'physical health'. Scores range from 0 to 100, with lower scores indicating better quality of life. A change in the physical health subscale score of 10 points or more is considered to be clinically meaningful The adjusted mean difference in Haem-A-QoL physical health subscale score between group A and group C was 12.5 points (95% CI −2.0 to 27.0, p=0.09, not statistically significant). The adjusted mean difference between group B

					and group C was 16.0 points (95% CI 1.2 to 30.8, considered non-significant due to the order of the outcomes in the hierarchical testing framework). In Mahlangu et al. (2018) there was no statistically significant difference in Haem-A-QoL physical health subscale score between either emicizumab group (1.5 mg/kg every week or 3.0 mg/kg every 2 weeks) compared to the no prophylaxis group. These results suggest that people treated with emicizumab do not have better health-related quality of life compared with people who received no prophylaxis. The study did not report on health-related quality of life in people treated with factor VIII prophylaxis.
Adverse events	Mahlangu et al. 2018 (HAVEN 3)	7/10	Directly applicable	B	543 adverse events were reported in 127/150 participants (85%) receiving emicizumab prophylaxis. The most common adverse events were injection-site reaction, arthralgia (joint pain) and nasopharyngitis. Fourteen serious adverse events were reported, including bleeding events, a cardiac disorder and infections. One person discontinued treatment with emicizumab due to a number of adverse events that were considered to be related to emicizumab. There were no deaths, no cases of thrombotic microangiopathy and no thrombotic events. There were no serious adverse events related to co-exposure to emicizumab and factor VIII. No new factor VIII inhibitors developed in participants receiving emicizumab. One person who had previously undergone immune tolerance induction had re-emergence of a detectable inhibitor at week 13 (1.6 Bethesda units), which was still detectable at week 25 (0.7 Bethesda units.
Development of anti-drug antibodies	Mahlangu et al. 2018 (HAVEN 3)	7/10	Directly applicable	B	No participants developed antibodies to emicizumab during the study by Mahlangu et al. (2018). However, the SPC for emicizumab states that 4 participants (2.1%) in the phase I/II clinical trials tested positive for anti-emicizumab antibodies, all of which were non-neutralising. These results suggest that the development of antibodies to emicizumab will be uncommon, although it should be noted that the development of emicizumab antibodies would have a large impact on a person's treatment.

3 Related NICE guidance and NHS England clinical policies

3.1 There are no specific NICE guidelines on this topic.

3.2 NHS England has published a Clinical Commissioning Policy for Immune Tolerance Induction [ITI] for haemophilia A.

3.3 NHS England has published a Clinical Commissioning Policy for Emicizumab as prophylaxis in people with congenital haemophilia A with factor VIII inhibitors (all ages)

3.4 A service specification for haemophilia services (all ages) commissioned by NHS England has been developed (B05/S/a).

4 References

Mahlangu J, Oldenburg I, Paz-Priel C et al. (2018) Emicizumab prophylaxis in patients who have hemophilia A without Inhibitors. New England Journal of Medicine 379(9): 811-822

This clinical evidence review has been written by NICE, following the process set out in the standard operating procedure.

Appendix 1 Search strategy

Database: Medline
Platform: Ovid
Version: Ovid MEDLINE(R) ALL <1946 to July 30, 2018>
Search date: 31st July 2018
Number of results retrieved: 31
Search strategy:

Database: Ovid MEDLINE(R) ALL <1946 to July 30, 2018>
---
1 Hemophilia A/ (19448)
2 (haemophil* or hemophil*).tw. (44993)
3 ((heredit* or inherit* or congen*) adj4 ("8" or VIII or eight) adj4 deficien*).tw. (77)
4 or/1-3 (48909)
5 emicizumab.tw. (31)
6 hemlibra.tw. (2)
7 (ACE910 or ACE-910 or "ACE 910").tw. (23)
8 (RG6013 or RG-6013 or "RG 6013").tw. (0)
9 or/5-8 (45)
10 4 and 9 (38)
11 limit 10 to english language (33)

Database: Medline in-process
Platform: Ovid
Version: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <July 30, 2018>
Search date: 31st July 2018
Number of results retrieved: 11

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <July 30, 2018>
---
1 Hemophilia A/ (0)
2 (haemophil* or hemophil*).tw. (2381)
3 ((heredit* or inherit* or congen*) adj4 ("8" or VIII or eight) adj4 deficien*).tw. (3)
4 or/1-3 (2382)
5 emicizumab.tw. (14)
6 hemlibra.tw. (1)
7 (ACE910 or ACE-910 or "ACE 910").tw. (4)
8 (RG6013 or RG-6013 or "RG 6013").tw. (0)
9 or/5-8 (14)
10 4 and 9 (12)
11 limit 10 to english language (11)

Database: Medline epubs ahead of print
Platform: Ovid
Version: Ovid MEDLINE(R) Epub Ahead of Print <July 30, 2018>
Search date: 31st July 2018
Number of results retrieved: 5
Search strategy:

Database: Ovid MEDLINE(R) Epub Ahead of Print <July 30, 2018>
---
1 Hemophilia A/ (0)

2 (haemophil* or hemophil*).tw. (475)
3 ((heredit* or inherit* or congen*) adj4 ("8" or VIII or eight) adj4 deficien*).tw. (3)
4 or/1-3 (475)
5 emicizumab.tw. (6)
6 hemlibra.tw. (0)
7 (ACE910 or ACE-910 or "ACE 910").tw. (1)
8 (RG6013 or RG-6013 or "RG 6013").tw. (0)
9 or/5-8 (7)
10 4 and 9 (5)
11 limit 10 to english language (5)

Database: Medline daily update
Platform: Ovid
Version: Ovid MEDLINE(R) Daily Update <July 30, 2018>
Search date: 31st July 2018
Number of results retrieved: 0
Search strategy

Database: Ovid MEDLINE(R) Daily Update <July 30, 2018>
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1 Hemophilia A/ (21)
2 (haemophil* or hemophil*).tw. (39)
3 ((heredit* or inherit* or congen*) adj4 ("8" or VIII or eight) adj4 deficien*).tw. (0)
4 or/1-3 (41)
5 emicizumab.tw. (0)
6 hemlibra.tw. (0)
7 (ACE910 or ACE-910 or "ACE 910").tw. (0)
8 (RG6013 or RG-6013 or "RG 6013").tw. (0)
9 or/5-8 (0)
10 4 and 9 (0)
11 limit 10 to english language (0)

Database: Embase
Platform: Ovid
Version: Embase <1974 to 2018 Week 31>
Search date: 31st July 2018
Number of results retrieved: 64
Search strategy:

Database: Embase <1974 to 2018 Week 31>
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1 hemophilia A/ (19944)
2 (haemophil* or hemophil*).tw. (58780)
3 ((heredit* or inherit* or congen*) adj4 ("8" or VIII or eight) adj4 deficien*).tw. (121)
4 or/1-3 (62346)
5 emicizumab/ (125)
6 emicizumab.tw. (77)
7 hemlibra.tw. (11)
8 (ACE910 or ACE-910 or "ACE 910").tw. (82)
9 (RG6013 or RG-6013 or "RG 6013").tw. (2)
10 or/5-9 (171)

11 4 and 10 (149)
12 limit 11 to english language (148)
13 limit 12 to (conference abstract or conference paper or "conference review" or erratum or letter or note or patent) (84)
14 12 not 13 (64)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); DARE; CENTRAL; HTA database; NHS EED
Platform: Wiley
Version:
CDSR –Issue 7 of 12, July 2018
DARE – 2 of 4, April 2015 (legacy database)
CENTRAL – Issue 4 of 12, June 2018
HTA – 4 of 4, October 2016 (legacy database)
NHS EED – 2 of 4, April 2015 (legacy database)
Search date: 29th May 2018
Number of results retrieved: CDSR – 0; DARE – 0 ; CENTRAL – 23; HTA – 0; NHS EED - 0.

Date Run: 31/07/18 13:02:40.645

ID SearchHits
#1 MeSH descriptor: [Hemophilia A] this term only 423
#2 haemophil* or hemophil*:ti,ab,kw (Word variations have been searched) 3236
#3 (heredit* or inherit* or congen*) near ("8" or VIII or eight) near deficien*:ti,ab,kw (Word variations have been searched) 4
#4 #1 or #2 or #3 3238
#5 emicizumab:ti,ab,kw (Word variations have been searched) 22
#6 hemlibra:ti,ab,kw (Word variations have been searched) 0
#7 ACE910 or ACE-910 or "ACE 910":ti,ab,kw (Word variations have been searched) 11
#8 RG6013 or RG-6013 or "RG 6013":ti,ab,kw (Word variations have been searched) 0
#9 #5 or #6 or #7 or #8 23
#10 #4 and #9 23

Appendix 2 Study selection

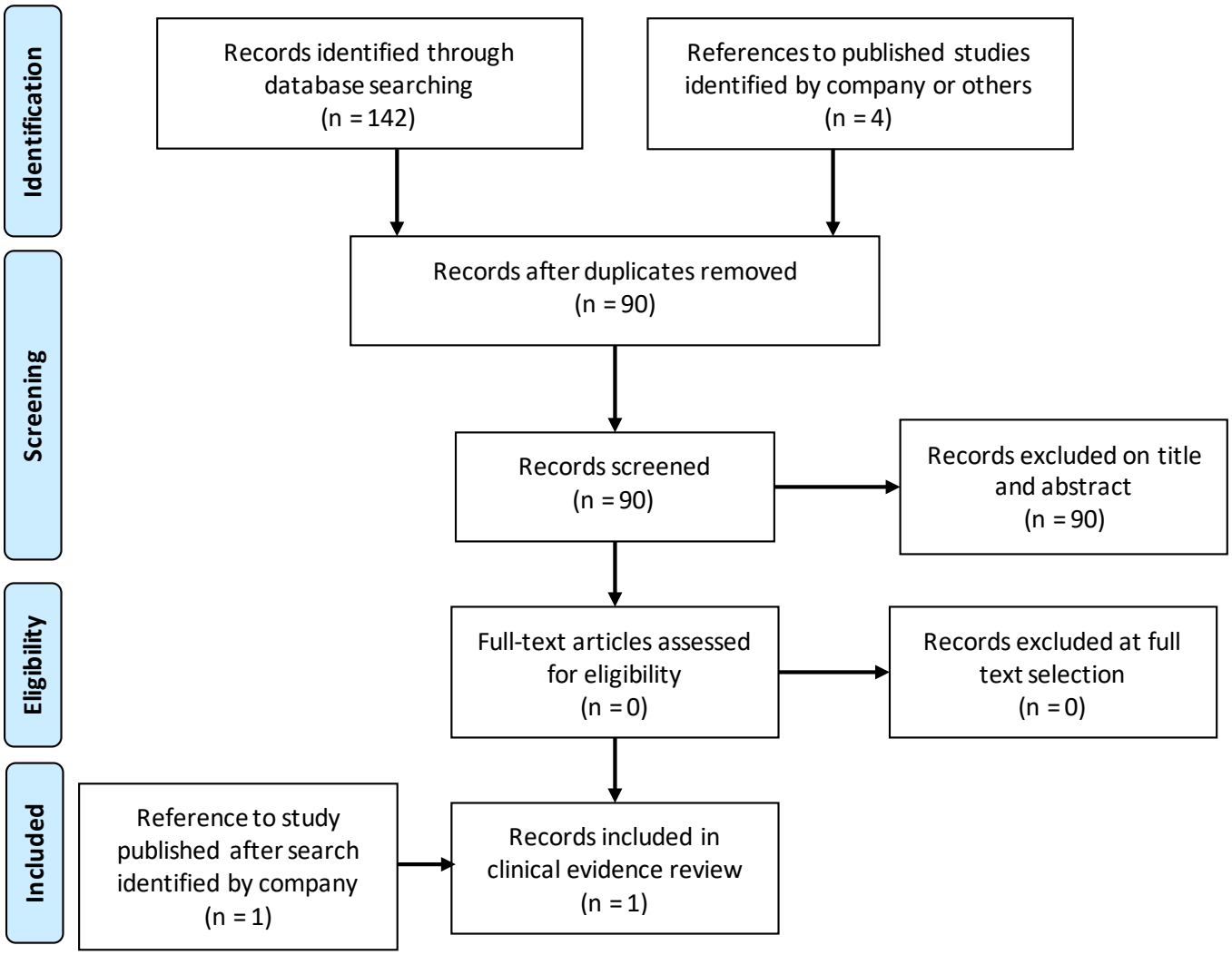
The search strategy presented in appendix 1 yielded 90 studies. These were screened on titles and abstracts in EPPI Reviewer according to the following inclusion/exclusion criteria:

Sifting criteria	Inclusion	Exclusion
Population		Non-humans
Intervention		
Comparator		
Outcomes		
Other		Abstracts Non-English language Duplicates Opinion pieces, commentaries, epidemiological studies, burden of disease studies

Table 4 Studies included at full text

No studies were included at full text.

Figure 1 Flow chart of included studies



Appendix 3 Evidence tables

Table 5 Mahlangu et al. 2018 (HAVEN 3 study)

Study reference	Mahlangu J, Oldenburg I, Paz-Priel C et al. (2018) Emicizumab prophylaxis in patients who have hemophilia A without inhibitors. New England Journal of Medicine 379(9): 811–822
Unique identifier	NCT02847637
Study type (and NSF-LTC study code)	Open-label, multicentre, phase III randomised controlled trial P1 Primary research using quantitative approaches
Aim of the study	To assess the efficacy, safety, and pharmacokinetics of emicizumab prophylaxis (given once weekly or every 2 weeks) in people with haemophilia A without inhibitors
Study dates	Started: September 2016 Primary completion date: September 2017 (data-cut off for analysis reported in Mahlangu et al. 2018)
Setting	44 centres in 14 countries, including 4 centres in the UK
Number of participants	152 enrolled 89 in the randomised groups (group A, B or C) 63 in the non-randomised group (group D), of whom 48 people had previously received prophylactic factor VIII in a non-interventional study
Population	People aged 12 years and over with severe congenital haemophilia A without current factor VIII inhibitors, who were receiving episodic (on-demand) or prophylactic factor VIII infusions
Inclusion criteria	Severe congenital haemophilia A (factor VIII activity <1% normal) Absence of current factor VIII inhibitors (<0.6 Bethesda units/ml, confirmed within 8 weeks of enrolment) in the previous 5 years (including individuals with successful completion of immune tolerance induction) Treatment with episodic or prophylactic factor VIII for 24 weeks or more before study entry 5 or more bleeding events with episodic factor VIII treatment in the past 24 weeks (no bleeding requirements for previous prophylaxis treatment)
Exclusion criteria	Any bleeding disorder other than haemophilia A Thromboembolic disease (any current signs or treatment within the past 12 months)
Intervention(s)	All groups had a loading dose Emicizumab 3.0 mg/kg once weekly for 4 weeks followed by maintenance dose of either: Emicizumab 1.5 mg/kg once weekly (group A) Emicizumab 3.0 mg/kg every 2 weeks (group B) Emicizumab 1.5 mg/kg once weekly (group D, non-randomised)
Comparator(s)	No prophylaxis (group C)

Length of follow-up	24 weeks
Outcomes	Primary outcome (for group A or group B compared with group C): • Rate of treated bleeding events (from baseline to at least 24 weeks); reported as annualised bleeding rate
	Secondary outcomes: • Rate of all bleeding events (treated and not treated) • Rate of spontaneous bleeding events • Rate of joint bleeding events • Quality of life, measured using the Haem-A-QoL physical health subscale • Intra-individual comparison of bleeding rates in people previously treated with factor VIII prophylaxis (48 people in group D, non-randomised)
	Exploratory outcomes: • Patient preference for treatment at week 17, measured using a survey developed by the investigators (EmiPref)
	Pharmacokinetic outcomes: • Trough emicizumab plasma concentration by dosing regimen
	Safety outcomes: • Adverse events • Serious adverse events • Thromboembolic events • Development of emicizumab antibodies or factor VIII inhibitors
Source of funding	F. Hoffmann–La Roche and Chugai Pharmaceutical

NSF-LTC

Criteria	Score	Narrative description of study quality
1. Are the research questions/aims and design clearly stated?	2/2	Clear and appropriate.
2. Is the research design appropriate for the aims and objectives of the research?	1/2	Design appropriate for study type, but the study is limited by the open-label design, lack of direct active comparator (for example, prophylactic factor VIII) and the inclusion of non-randomised participants. This may have introduced bias, particularly for the subjective outcomes, such as quality of life and patient preference.

3. Are the methods clearly described?	2/2	Clear and appropriate.
4. Are the data adequate to support the authors' interpretations / conclusions?	1/2	Results partially support the author's conclusions. The authors conclude that emicizumab is associated with lower bleed rates compared with no prophylaxis. Although the study included people who had previously received prophylactic treatment with factor VIII who went on in HAVEN3 to receive emicizumab, these people were not randomised and the study was not designed to compare these people with those receiving no prophylaxis. . Although the author's report intra-individual comparisons of emicizumab with factor VIII, such comparisons have limitations, and firm conclusions on the relative effectiveness of emicizumab cannot be made.
5. Are the results generalisable?	1/2	The study was limited to people with severe haemophilia A (factor VIII activity <1%). The results may not be generalisable to people with moderate haemophilia A (factor VIII activity 1-5%) and a high risk of bleeding. Although the study included people previously treated with episodic and prophylactic factor VIII, the study was not designed to assess the efficacy of emicizumab in people previously treated with prophylactic factor VIII. The results for people previously treated with episodic factor VIII (groups A, B and C) may not be generalisable to those people who had taken prophylactic factor VIII.

Total	7/10	
Applicability*	Directly applicable	The intervention and indication are directly relevant to the decision problem

Appendix 4 Results tables

Table 6 Mahlangu et al. 2018 (HAVEN 3 study)

Group	Emicizumab 1.5 mg/kg every week (Group A)	Emicizumab 3.0 mg/kg every 2 weeks (Group B)	No prophylaxis, control (Group C)	Analysis
N	**36**	**35**	**18**	
Primary outcome				
Annualised rate of bleeding events treated with factor VIII	1.5 events (95% CI 0.9 to 2.5)	1.3 events (95% CI 0.8 to 2.3)	38.2 events (95% CI 22.9 to 63.8)	Significantly lower bleeding rates for both emicizumab treatment regimens compared with no prophylaxis Group A vs. C: RR 0.04 (95% CI 0.02 to 0.08, p<0.001) Group B vs. C: RR 0.03 (95% CI 0.02 to 0.07, p<0.001)
Secondary outcomes				
Annualised rate of all bleeding events, irrespective of treatment with factor VIII	2.5 events (95% CI 1.6 to 3.9)	2.6 events (95% CI 1.6 to 4.3)	47.6 events (95% CI 28.5 to 79.6)	Significantly lower bleeding rates for both emicizumab treatment regimens compared with no prophylaxis Group A vs. C: RR 0.05 (95% CI 0.03 to 0.10) Group B vs. C: RR 0.06 (95% CI 0.03 to 0.10)
Annualised rate of spontaneous bleeding events treated with factor VIII	1.0 events (95% CI 0.5 to 1.9)	0.3 events (95% CI 0.1 to 0.8)	15.6 events (7.6 to 31.9)	Significantly lower bleeding rates for both emicizumab treatment regimens compared with no prophylaxis Group A vs. C: RR 0.06 (0.03 to 0.15) Group B vs. C: RR 0.02 (0.01 to 0.06)
Annualised rate of joint bleeding events	1.1 events (95% CI 0.6 to 1.9)	0.9 events (95% CI 0.4 to 1.7)	26.5 events (14.7 to 47.8)	Significantly lower bleeding rates for both emicizumab treatment

treated with factor VIII				regimens compared with no prophylaxis Group A vs. C: RR 0.04 (95% CI 0.02 to 0.09) Group B vs. C: RR 0.03 (95% CI 0.02 to 0.07)
Annualised rate of target-joint bleeding events treated with factor VIII	0.6 events (95% CI 0.3 to 1.4)	0.7 events (95% CI 0.3 to 1.6)	13.0 events (95% CI 5.2 to 32.3)	Significantly lower bleeding rates for both emicizumab treatment regimens compared with no prophylaxis Group A vs. C: RR 0.05 (95% CI 0.02 to 0.14) Group B vs. C: RR 0.05 (95% CI 0.02 to 0.15)
Haem-A-QoL physical health subscale score at week 25	Not reported	Not reported	Not reported	No significant difference in health-related quality of life for either emicizumab treatment regimen compared with no prophylaxis Group A vs. C: Adjusted mean difference between groups= 12.5 points (95% CI −2.0 to 27.0, p=0.09) Group B vs. C: Adjusted mean difference between groups= 16.0 points (95% CI 1.2 to 30.8, considered non-significant due to the order of the outcomes in the hierarchical testing framework)

Exploratory outcome					
Patient preference for treatment, assessed using the EmiPref Survey	Not reported	Not reported	Not reported	The EmiPref survey was completed by 71% (95/134) of eligible participants. Across all respondents, 94% (95% CI 87 to 98) preferred emicizumab, with 45/46 of participants in group D preferring emicizumab to factor VIII prophylaxis (98%, 95% CI 88 to 100)	
Safety (only reported in participants receiving emicizumab)					
Group	**Emicizumab 1.5 mg/kg every week (Group A)**	**Emicizumab 3.0 mg/kg every 2 weeks (Group B)**	**Emicizumab 3.0 mg/kg every 2 weeks (Group C)[1]**	**Emicizumab 1.5 mg/kg every week (Group D)[2]**	**Total**
N	**36**	**35**	**16**	**63**	**150**
Median duration of treatment (range)	29.3 weeks (17.3 to 49.1)	30.1 weeks (6.1 to 50.1)	7.1 weeks (0.1 to 26.1)	33.1 weeks (18.0 to 48.1)	29.0 weeks (0.1 to 50.1)
Number of adverse events	143	145	19	236	543
Number of serious adverse	1	3	0	10	14
Number of participants who stopped treatment due to adverse events (%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)	1 (1%)
Most common adverse events (%)					
Injection-site reaction	9 (25%)	7 (20%)	2 (12%)	20 (32%)	38 (25%)
Upper respiratory tract infection	4 (11%)	4 (11%)	0 (0%)	8 (13%)	16 (11%)
Nasopharyngitis	2 (6%)	6 (17%)	0 (0%)	10 (16%)	18 (12%)
Arthralgia	7 (19%)	6 (17%)	1 (6%)	14 (22%)	28 (19%)

Headache	3 (8%)	4 (11%)	1 (6%)	8 (13%)	16 (11%)
Influenza	1 (3%)	3 (9%)	0 (0%)	5 (8%)	9 (6%)

Notes

[1] After 24 weeks or longer, participants in group C could switch emicizumab every 2 weeks (and remain in group C). Safety outcomes only reported during the emicizumab treatment phase.

[2] Group D included 63 people who had previously received prophylactic factor VIII, who were allocated in a non-randomised fashion to emicizumab 1.5 mg/kg once weekly

Abbreviations: RR, relative risk

Appendix 5 Grading of the evidence base

Each study is assigned one of the following codes:

NSF-LTC Categories of research design

Primary research based evidence
P1 Primary research using quantitative approaches
P2 Primary research using qualitative approaches
P3 Primary research using mixed approaches (quantitative and qualitative)
Secondary research based evidence
S1 Meta-analysis of existing data analysis
S2 Secondary analysis of existing data
Review based evidence
R1 Systematic reviews of existing research

For each key outcome, studies were grouped and the following criteria were applied to achieve an overall grade of evidence by outcome.

Grade	**Criteria**
Grade A	More than 1 study of at least 7/10 quality and at least 1 study directly applicable
Grade B	One study of at least 7/10 which is directly applicable OR More than one study of a least 7/10 which are indirectly applicable OR More than one study 4-6/10 and at least one is directly applicable OR One study 4-6/10 which is directly applicable and one study of least 7/10 which is indirectly applicable
Grade C	One study of 4-6/10 and directly applicable OR Studies 2-3/10 quality OR Studies of indirect applicability and no more than one study is 7/10 quality

Applicability should be classified as:

- Direct studies that focus on people with the indication and characteristics of interest.

- Indirect studies based on evidence extrapolated from populations with other conditions and characteristics.