NICE National Institute for Health and Care Excellence

NICE guidance

Marstacimab for treating severe haemophilia A or B in people 12 years and over without anti-factor antibodies

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do 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.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

Haemophilia B

1.1 Marstacimab is recommended, within its marketing authorisation, as an option for preventing bleeding episodes caused by severe (factor IX [9] activity less than 1%) haemophilia B (congenital factor 9 deficiency) in people 12 years and over who:

- weigh at least 35 kg and
- do not have factor 9 inhibitors (anti-factor antibodies).

Marstacimab is only recommended if the company provides it according to the commercial arrangement.

Haemophilia A

1.2 Marstacimab is not recommended, within its marketing authorisation, for preventing bleeding episodes caused by severe (factor VIII [8] activity less than 1%) haemophilia A (congenital factor 8 deficiency) in people 12 years and over who weigh at least 35 kg and do not have factor 8 inhibitors.

1.3 This recommendation is not intended to affect treatment with marstacimab that was started in the NHS before this guidance was published. People having treatment outside this may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop. For children or young people, this decision should be made jointly by the healthcare professional, the child or young person, and their parents or carers.

Why the committee made these recommendations

Treatment for preventing bleeding episodes (prophylaxis) is usually factor 8 replacement

therapy or emicizumab in severe haemophilia A, and factor 9 replacement therapy in severe haemophilia B.

In severe haemophilia A and B, evidence from a clinical trial shows marstacimab reduces the number of bleeding episodes a person has compared with factor 8 or 9 prophylaxis. In severe haemophilia A, there is no trial directly comparing marstacimab with emicizumab. An indirect comparison suggests marstacimab reduces bleeding episodes by a similar number as emicizumab. But the evidence for this is uncertain.

In severe haemophilia B, the cost-effectiveness evidence for marstacimab showed it is a cost-effective option compared with factor 9. So, marstacimab is recommended for preventing bleeding episodes caused by severe haemophilia B.

In severe haemophilia A, the cost-effectiveness evidence for marstacimab showed it is not a cost-effective option compared with factor 8 and emicizumab. So, marstacimab is not recommended for preventing bleeding episodes caused by severe haemophilia A.

2 Information about marstacimab

Marketing authorisation indication

2.1 Marstacimab (Hympavzi, Pfizer) is indicated for 'routine prophylaxis of bleeding episodes in patients 12 years of age and older, weighing at least 35 kg, with:

- severe haemophilia A (congenital factor VIII deficiency, FVIII <1%) without factor VIII inhibitors, or
- severe haemophilia B (congenital factor IX deficiency, FIX <1%) without factor IX inhibitors'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for marstacimab.

Price

2.3 The list price of marstacimab is confidential until published by the Department for Health and Social Care.

2.4 The company has a commercial arrangement (simple discount patient access scheme). This makes marstacimab available to the NHS with a discount. The size of the discount is commercial in confidence.

Carbon Reduction Plan

2.5 For information, the Carbon Reduction Plan for UK carbon emissions is published on the company's webpage on marstacimab (PDF only).

3 Committee discussion

The evaluation committee considered evidence submitted by Pfizer, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

3.1 Haemophilia A and B are caused by gene mutations that result in the inability or reduced ability to produce factor VIII for haemophilia A and factor IX for haemophilia B, which are vital for blood clotting. This leads to prolonged bleeding after injury and, when severe, bleeding into joints and muscles without any injury. Haemophilia A and B are X-linked recessive inherited disorders that mostly occur in men and boys. Women and girls who carry the haemophilia gene mutation may have mild or, rarely, moderate to severe symptoms of bleeding. For this evaluation, the company presented evidence of clinical and cost effectiveness for marstacimab in severe haemophilia A and B only in people who do not have anti-factor antibodies. The severity of haemophilia A and B is classed according to the amount of clotting factor compared with expected levels. Severe haemophilia is defined as having less than 1% of clotting factor present. The clinical experts explained that severe haemophilia A and B usually present in the first few years of life with joint or muscle bleeds. Occasionally, this may cause spontaneous and potentially fatal bleeds. The clinical experts explained that subclinical bleeds are also associated with the condition. These bleeds can cause chronic pain and damage joints, potentially affecting mobility and, over time, cause the need for surgery. The patient experts explained that the risk of bleeding can limit jobs, sports and other activities. They explained that factor prophylaxis for severe haemophilia requires intravenous injection, self-administered or administered by carers, as often as every 2 to 3 days. This is a substantial treatment burden. Factor prophylaxis is also associated with a substantial negative psychological effect on people with the condition and is associated with a worsened quality of life of carers of children with the condition. Because haemophilia A and B are inherited, there may be several siblings with the condition in the same family, increasing its impact on carers. The committee recognised that severe haemophilia A and B are chronic conditions that substantially affect people's

lives.

Clinical management

Treatment pathway

3.2 The clinical experts explained that the main aim of treatment for severe haemophilia A and B is to prevent bleeding and long-term damage, especially to joints. This is achieved through prophylaxis (treatment used on a regular basis to prevent bleeds) and 'on-demand' treatment (used when needed if bleeding occurs, such as after an injury). The available treatment options for haemophilia A for long-term prophylaxis are factor VIII replacement therapy, given as intravenous injection, to replenish missing clotting factor in the blood, and emicizumab given as a subcutaneous injection. Emicizumab, a non-factor VIII treatment, is commissioned through an NHS England clinical commissioning policy as prophylaxis for severe congenital haemophilia A in people of all ages without anti-factor antibodies. Emicizumab is a monoclonal antibody administered every 1 to 4 weeks and mimics the activity of factor VIII to restore clotting function. The available treatment option for haemophilia B for long-term prophylaxis is factor IX replacement therapy, through intravenous injection. Currently, there are no subcutaneous treatment options available for people with haemophilia B. For both severe haemophilia A and B, standard and extended half-life factor replacement therapies are available and extra on-demand factor replacement therapy can also be used for treating bleeds. The committee noted that NICE's technology appraisal guidance on etranacogene dezaparvovec for treating moderately severe or severe haemophilia B recommended it through a managed access programme. But etranacogene dezaparvovec is not a relevant comparator in this evaluation. The committee concluded that treatment for severe haemophilia A includes prophylaxis with factor VIII replacement therapy or emicizumab, and treatment for severe haemophilia B includes prophylaxis with factor IX replacement therapy.

Limitations of the current treatment options

3.3 The clinical and patient experts explained that current treatment options do not always prevent bleeding and are associated with challenges in administering them. Frequent injections for factor replacement therapy can damage veins, resulting in pain on administration and increasing the chance of a vein 'collapsing'. The frequency of injections is especially challenging in older people and young children who may have poor venous access. The patient experts stated that as they have become older, they are limited on which veins they can use because of scar tissue. This can make treatment more painful and difficult to administer. Also, about 5% to 7% of people with haemophilia A develop antibodies (inhibitors) to factor VIII and about 5% of people with haemophilia B develop antibodies to factor IX. Anti-factor antibodies make factor replacement therapies less effective. The committee heard that people with anti-factor antibodies, particularly those with severe haemophilia B, have limited treatment options. The clinical experts explained that the outcomes for these individuals are worse compared with people who do not develop antibodies. They may be wheelchair bound by their second decade because of increased bleeds in the joints. The committee noted that because of the anticipated marketing authorisation, people with anti-factor antibodies are outside the scope of this appraisal (see section 2.1). In the NHS, most people with severe haemophilia A (without anti-factor antibodies) are offered emicizumab, an alternative to factor replacement therapy, which is administered subcutaneously. The patient experts explained that there is no single best treatment option for everybody; different people will value aspects of treatment options differently. For example, some people will value a subcutaneous option, while others value an intravenous option. People who participate in sports, for example, may prefer intravenous options so they can have flexibility in adjusting their required dose. The committee acknowledged there are no subcutaneous treatment options available for severe haemophilia B. It concluded that new treatment options for severe haemophilia A and B would be welcomed.

Clinical evidence

BASIS trial

3.4 The clinical evidence for marstacimab came from BASIS, an unpublished phase 3 open-label non-randomised one-way non-inferiority crossover trial comparing the 'before' and 'after' crossover periods. This enrolled people 12 years and over with severe haemophilia A or severe haemophilia B who had no antibodies to factor VIII or IX. The observational phase enrolled 128 people who previously had either:

- factor VIII or factor IX prophylaxis and who had at least 80% adherence with the scheduled prophylaxis regimen during the 6 months before enrolment (n=91), or
- on-demand treatment with 6 or more acute bleeding episodes that required coagulation factor injections during the 6 months before enrolment and would be willing to continue on-demand treatment during the observational phase (n=37).

The active treatment phase included 83 people who had used factor VIII or IX prophylaxis in the observational phase. They had 300 mg of marstacimab as a loading dose followed by 150 mg once weekly, self-administered by subcutaneous prefilled syringe injection. After 6 months, people could have their dose increased to 300 mg once weekly. This was decided by a clinician based on the dose escalation criteria:

- body weight at least 50 kg
- at least 2 spontaneous bleeds in a 6-month period treated with on-demand factor VIII or IX.

The primary outcome in BASIS was the annualised bleeding rate (ABR) for treated bleeds through the observational phase and active treatment phase. The non-inferiority margin was 2.5 bleeds per year. The committee understood that if non-inferiority of marstacimab compared with factor prophylaxis was shown, then superiority was tested. Key secondary outcomes included annualised joint bleeding rate, spontaneous bleeds, target joint bleeds and total bleeds (treated and untreated) at 12 months after

starting marstacimab. The number of people with no treated bleeds was recorded. The company also included data from an open-label extension study of 75 people who had prophylaxis for 6 months before BASIS and continued to have factor prophylaxis during the observational phase.

The committee noted that the BASIS trial design was not aligned with UK practice. The committee concluded that the relevant evidence for marstacimab came from BASIS and its open-label extension study. But it noted these limitations with the trial design:

- no randomisation within the trial
- being open label, there could be a differential reporting of bleeds
- no UK trial sites (see section 3.6)
- emicizumab was not permitted in the observational phase of the trial, but this is a relevant comparator for people with severe haemophilia A in the NHS
- for people who had routine factor replacement prophylaxis, the proportion who had standard half-life or extended half-life was not reflective of the proportions used in the NHS (see section 3.6).

The committee considered these limitations led to important uncertainties including the trial results (see section 3.5), generalisability (see section 3.6) and the use of ABR data in the model (see section 3.9).

Trial results

3.5 The company presented results from the end of the 6-month observational phase and 12-month active treatment phase of BASIS, and results for a data cut from the open-label extension study. The EAG advised that dose escalation occurred after 6 months of the active treatment phase and the 12-month results presented by the company for the active treatment phase were censored for dose escalations. The EAG requested additional data at 6 months to view results before any dose escalation happened. The BASIS trial demonstrated an improvement with marstacimab over factor prophylaxis, as measured by the ABR

of treated bleeds. The mean model-derived ABR for treated bleeds was 5.08 (95% confidence interval [CI] 3.40 to 6.77) for marstacimab during the 12-month active treatment phase compared with 7.85 (95% CI 5.09 to 10.61) for routine prophylaxis during the 6-month observational phase. This represented a reduction in estimated ABR for treated bleeds of 2.77 (95% CI -5.37 to -0.16). The mean ABR for treated bleeds in haemophilia A was 5.30 for marstacimab during the 12-month active treatment phase compared with 9.16 for routine prophylaxis during the 6-month observational phase. For haemophilia B, the mean ABR for treated bleeds was 4.71 for marstacimab during the 12-month active treatment phase compared with 3.26 for routine prophylaxis during the 6-month observational phase. Six people with haemophilia B increased their dose of marstacimab during the active treatment phase. The mean ABR for treated bleeds for all 18 people with haemophilia B was 3.88 for marstacimab. People having marstacimab had a reduction in ABR for treated joint bleeds from baseline.

Generalisability

3.6 BASIS and its open-label extension were multicentre studies across 19 countries and included sites in Europe. The EAG raised concerns that no UK sites were included. The committee considered the impact of non-UK sites on factor prophylaxis usage in BASIS. The clinical experts advised that in other countries people may have a different history of prophylaxis treatment compared with the UK, which could mean much higher baseline bleed rates. They noted that people with higher background bleed rates who have experienced joint bleeds are more likely to bleed into that joint again, compared with those who have never had a joint bleed. The patient experts noted that people in the UK have optimal factor prophylaxis from a young age. This typically results in a very low bleeding frequency and fewer target joint bleeds. The committee noted several countries were included in the trial, and some may not manage bleeds as optimally. The EAG noted that data was not available to identify countries in BASIS that may have a similar treatment approach to the NHS. It also noted that BASIS included different proportions of people having standard half-life and extended half-life treatment compared with data from the UK Haemophilia Centre Doctors' Organisation (UKHCDO) and the exact results were considered confidential. The clinical experts stated people in BASIS were not on factor prophylaxis that is comparable to standard of care in the NHS. The EAG also noted that baseline

ABRs were much higher during the observational phase compared with in the NHS. The committee concluded that there are substantial concerns about trial generalisability and that bleed rates were likely to be much higher than in UK practice. The committee further concluded that the effect of marstacimab may have been overestimated compared with its potential effect in UK clinical practice. It also concluded that the trial generalisability may have implications for the results used in the model.

Indirect treatment comparison

Comparison with emicizumab

3.7 Emicizumab is a subcutaneous treatment option for severe haemophilia A. There were no trials directly comparing marstacimab with emicizumab, so the company did an indirect treatment comparison (ITC) to establish the relative efficacy as measured by ABRs. The clinical-effectiveness data for emicizumab came from HAVEN-3. HAVEN-3 was an open-label study including 152 people aged 12 years and over with severe haemophilia A and no anti-factor antibodies. It had 4 arms, including people who:

- had on-demand regimens (instead of factor prophylaxis), randomised to have 1.5 mg/kg emicizumab weekly (arm A), 3 mg/kg every 2 weeks (arm B) or no prophylaxis (arm C)
- had prophylaxis regimens, who had 1.5 mg/kg emicizumab weekly (arm D).

Only arm D was included in the ITC because this group had previously used factor VIII prophylaxis. The company did not have access to individual patient data from HAVEN-3, so it did an unanchored simulated treatment comparison (STC). The STC analysis was based on bleed rates for all participants and did not distinguish between people who did and did not experience bleeds. The analysis accounted for effect modifiers and prognostic variables of previous ABRs (total rate), target joints (yes or no), age (years), body mass index (BMI) and ethnicity. The EAG advised that these differed from a published study from Astermark et al. 2023 that identified medically relevant covariates from HAVEN-3. These included age, ethnicity, BMI, baseline ABR, proportion of

people with fewer than 9 bleeds in the previous 24 weeks and proportion having standard half-life factor VIII replacement therapy. The company did another STC analysis using these covariates and included target joints in the STC adjustment. These analyses used only the first 33 weeks of follow up from BASIS for consistency with the reported follow-up data available for HAVEN-3. The EAG did its own network meta-analysis (NMA) using data from BASIS and HAVEN-3, in which the follow-up data for the observation and active treatment phases is limited to 6 months. This produced similar results to the STC. The results of the unanchored STC, using the company's preferred assumptions, suggested there were no statistical differences between marstacimab and emicizumab for total ABR. Using the STC covariates from Astermark et al. (2023), bleed rate ratios were closer to 1. The EAG's NMA had similar results. Exact results cannot be reported because the company marked them as confidential. The EAG advised that neither BASIS nor HAVEN-3 were designed to be compared in this way, and it is possible that differences in treatment effect may exist that have not been detected in these analyses. The committee decided that the indirect comparisons were highly uncertain. It concluded that the available evidence did not suggest marstacimab's effectiveness is markedly different to emicizumab, but the results are highly uncertain.

Economic model

Company's economic model

3.8 The company developed a 3-state Markov model to determine the cost effectiveness of marstacimab. The health states were 'no bleeds', 'bleeds' and 'death'. Patients could transition between the 'bleeds' and 'no bleeds' health states. All people entering the model were distributed among the 'no bleeds' and 'bleeds' health states. People having factor prophylaxis or marstacimab were distributed based on the BASIS observational and active treatment phase results, respectively, for the proportion of people with zero treated bleeding events. Within the 'bleeds' health state, both joint and non-joint bleeds were considered. The company estimated ABR for treated bleeds and annualised joint bleed rate for treated joint bleeds were estimated from a post-hoc analysis of BASIS data

for factor prophylaxis and marstacimab, and evidence from the company's ITC for the ABR for emicizumab. In the factor prophylaxis and emicizumab arms, distribution across the 'no bleeds' and 'bleeds' health states was unchanged across the model time horizon. People were assumed to remain on treatment. In the marstacimab arm of the model, the company assumed that the distribution of people in each health state remained constant over time while on treatment, and also assumed that people later redistributed across these health states to model stopping treatment. The company chose a cycle length of 1 year with a half-cycle correction and a time horizon of 64 years. Some people transitioned to death, aligned with general population mortality. That is, no mortality benefit was assumed for marstacimab and people with severe haemophilia A or B were assumed to have the same mortality as the general population. Treated bleeds were associated with a utility decrement per joint and non-joint bleed, and each bleed was associated with a cost. The company modelled a utility decrement per administration for subcutaneous treatments, marstacimab and emicizumab, and for intravenous treatments, factor VIII and factor IX replacement therapies. The committee concluded that the company's model structure was appropriate for decision making.

Treatment effectiveness in the model

3.9 The company's base case used the BASIS data to inform the ABRs of marstacimab and factor prophylaxis treatments and the ITC to inform the bleeding rates of emicizumab compared with marstacimab. The EAG advised that prophylaxis treatments used in BASIS did not reflect NHS standard of care (see section 3.6) and the results of the ITC were highly uncertain (see section 3.7). The EAG decided that the UKHCDO data was the best source to inform the ABRs of factor prophylaxis and emicizumab. It calculated estimates of bleed rates across the adult group and 12 years and over age groups using weighted averages. The results using the UKHCDO data are confidential and cannot be reported. The UKHCDO uses Haemtrack, a database used by people with haemophilia to record when they experience a bleed. The EAG calculated baseline ABRs for treated bleeds by combining the reported ABR from the UKHCDO report with the balance of standard half-life and extended half-life factor prophylaxis used in BASIS. It then derived a real-world UK-specific baseline ABR estimate for the BASIS population. Bleeding rates for marstacimab were

calculated by applying relative-effectiveness estimates from BASIS to the real-world UK-specific baseline ABR estimate. This estimate was used when applying the relative effects as estimated from BASIS to derive the efficacy of marstacimab. At the first committee meeting, the committee considered whether the UKHCDO dataset is reliable because it relies on people self-reporting. The clinical experts confirmed that the UKHCDO data is broadly reflective of bleed rates in the NHS. The patient experts stated that recording bleeding episodes on Haemtrack has become easier because it can now be done through an app on a mobile device. So, people are more likely to record bleeds compared with previous methods of recording. The committee noted the limitations associated with BASIS and the uncertainty in the company ITC. It accepted the views of the clinical and patient experts that UKHCDO is a reliable source of self-reported bleed rates. The committee concluded that using the UKHCDO baseline ABR for factor prophylaxis and emicizumab is preferable compared with those obtained from BASIS and the ITC. This is because it is more reflective of NHS practice. At consultation, the company updated its base case to align with the committee's preference.

Dose escalation of marstacimab

3.10 The BASIS trial protocol allowed dose escalation after 6 months in the active treatment phase and dose escalation could continue in the open-label extension study. People who dose escalated had their dose of marstacimab increased from 150 mg to 300 mg. A clinician decided whether a person dose escalated once they met the dose escalation criteria defined in the trial; not everybody who met the criteria dose escalated. The company's base case included dose escalation only in the first year of the model, and this was modelled as 13.25%. The model captured a clinical benefit of dose escalation, but people could not revert to the original dose because ABR for treated bleeds is modelled as constant thereafter. The EAG adjusted the percentage of dose escalation to reflect that nobody who dose escalated stopped treatment, so this figure is higher than the company's estimate. The EAG noted that people were able to dose escalate during the open-label extension study, which is beyond year 1 and therefore not captured in the model. So, the EAG's base case modelled dose escalation for year 2 of the model. The patient experts explained that, in the NHS, dose escalation may take more than a year to implement because people would have a conversation with their

clinician and choices around dose escalation are complex. The committee noted that decisions about dose escalation may depend on bleeding rates. It acknowledged that the modelled ABRs were lower using the UKHCDO data (see section 3.6) and that using this data may lead to a lower rate of dose escalation compared with the rate used in the company model. Clinical experts confirmed that some NHS clinical settings have zero tolerance for bleeding episodes, so dose escalation could be higher with this practice. If a person had 2 spontaneous bleeds in a 6-month period on a treatment, they could either dose escalate or stop treatment and have factor prophylaxis. The company stated that dose escalation varied between sites in the trial, but this data was not available for the committee. The patient experts explained that in the case of emicizumab, people accept a lower treatment efficacy compared with factor prophylaxis because they value the ease of subcutaneous administration compared with factor VIII administration. So, people may be willing to dose escalate rather than switch treatments to have the benefit of subcutaneous injections. At the first committee meeting, the committee concluded that there is uncertainty about the proportion of people who would dose escalate in the NHS. It noted that the dose escalation rate could be higher or lower than the rate assumed by the company. It recognised that dose escalation may occur beyond year 1, so preferred the EAG's base-case assumption of including dose escalation in the second year of the model to reflect the trial evidence. At consultation, the company updated its base case to align with the committee's preference.

Treatment discontinuation

3.11 The company's model assumed that people could stop marstacimab and switch to factor prophylaxis. The company applied a one-off discontinuation rate for marstacimab of 6.02% in the first cycle based on the rates of discontinuation in BASIS. This one-off discontinuation rate applied to people with haemophilia A and B in the model. For people with haemophilia A, the company stated it did not apply a discontinuation rate for emicizumab because of a lack of data availability. The EAG advised that this is a source of uncertainty and probable bias. The EAG retained this assumption in its base case, but presented a scenario that removed the discontinuation rate for marstacimab so neither treatment was stopped. This increased the incremental cost-effectiveness ratio (ICER) for marstacimab. The clinical expert confirmed that about 10% of people with haemophilia A stop using

emicizumab. The committee concluded that this is a source of uncertainty in the company's modelling, and that some people on emicizumab would also likely stop treatment. At the first committee meeting, the committee requested further analyses from the company to model a plausible scenario, matching UK practice, that is coherent between the discontinuation of marstacimab and emicizumab. This should include a scenario of applying a treatment discontinuation rate of 10% for emicizumab. At consultation, the company updated its base case and assumed that dose discontinuation of emicizumab and marstacimab was equal. The company's base case applied a one-off discontinuation rate for emicizumab of 6.02% in the first cycle. The company consulted clinical experts who confirmed that the discontinuation rate for emicizumab for people with haemophilia A in the UK ranged between 2% and 10%. The exact discontinuation rate of emicizumab in the UK is unknown. The company provided a scenario using a 10% discontinuation rate for emicizumab and marstacimab. The EAG agreed it is plausible that the discontinuation rate of emicizumab and marstacimab is equal. After consultation, the EAG's base case also assumed a discontinuation rate of 6.02% for emicizumab and marstacimab. At the second meeting, the committee concluded that it is reasonable to assume the discontinuation rate for emicizumab and marstacimab is equal and a rate of 6.02% is appropriate for decision making.

Dosing of factor prophylaxis

3.12 The company did not use the BASIS data to estimate the dosage of factor prophylaxis in its base case. The company took the summaries of product characteristics (SmPC) recommended dosage and weighted them by market shares estimated by IQVIA, a global healthcare company providing real-world data. The company also assumed drug wastage and dosing and rounded up these figures. The EAG advised that the dosing figures for factor prophylaxis in the company's base case were 18% higher compared with the mean total prophylaxis dose in the BASIS trial. The EAG did an analysis using the proportion of people having standard half-life and extended half-life factor prophylaxis in BASIS split by haemophilia A and B and applied these weights using IQVIA market share data. This showed a mean total prophylaxis dose 21% higher than the value in BASIS. The EAG suggests this result is either because dosing during BASIS was lower than in the NHS (which may imply suboptimal treatment during the

observational phase) or routine prophylaxis dosing in the model is too high. The EAG explored the second option by reducing the total factor prophylaxis dosing to 75% of the company's estimates. The clinical experts confirmed that they use SmPC recommendations for factor dosing because they want to aim for zero bleeds, so dosing is at the higher end of the recommendations. The company stated that their methods of using SmPC dosing aligned with NICE's technology appraisal guidance on etranacogene dezaparvovec for treating moderately severe or severe haemophilia B. The EAG noted that the total factor VIII issued per person per year in the model was higher compared with figures in the UKHCDO annual report. The EAG also noted that UKHCDO included factor VIII used for both routine prophylaxis and treating bleeds, but the company's estimates only included factor VIII used for routine prophylaxis. The committee considered both the company's and EAG's approaches. It noted the company may have overestimated dosing of factor prophylaxis compared with the UKHCDO data, which it considered was representative of NHS practice. It concluded that it preferred the EAG's base-case assumption of reducing the factor dosing to 75% of the company's base case. At consultation, the company stated that to achieve a zero bleed rate, clinicians in the NHS would dose at the upper limit of the SmPC recommendations. The company acknowledged that the UKHCDO data suggested a lower dose of factor prophylaxis is given. The company highlighted that a limitation of the UKHCDO dataset is that a small proportion of people do not use factor prophylaxis but instead take on-demand treatment for bleeding episodes. Patients having on-demand therapy would lower the average annual dose of factor prophylaxis products. The clinical experts noted that this detail was not available from the dataset but estimated it was likely that less than 5% of patients included in the UKHCDO dataset would be having on-demand factor therapy. The clinical experts explained that in younger patients dosing of factor prophylaxis is at the upper end of the recommended dose range, but as patients become older this may not always be the case because the half-life (time it takes for the treatment to leave the body) increases. At consultation the company updated its base case. It reduced the total factor prophylaxis dosing to 85% of its original base case to align with the level of dosing observed in BASIS. The EAG retained its original base case that reduced the factor dosing to 75% of the company's base case. The committee concluded that the EAG's base-case assumption of reducing the factor dosing to 75% of the company base case remained its preference.

Separate or pooled modelling

3.13 The company presented a single model for haemophilia A and B, which used the pooled ABR effectiveness estimates for haemophilia A and B. But the company's base case presented results for marstacimab compared with treatments for haemophilia A and B separately (see section 3.21). The company stated that BASIS and its open-label extension were not powered to detect differences in ABRs of marstacimab between haemophilia A or B (which were subgroups of the trial population). Marstacimab had a smaller treatment effect for severe haemophilia B compared with severe haemophilia A (see section 3.5). The company and EAG both provided scenario analyses using the separate estimates of clinical effectiveness for haemophilia A and B. The clinical experts at the first committee meeting noted there is likely no biological reason why marstacimab would be less effective for severe haemophilia B. The committee noted that the confidence intervals for haemophilia B crossed the boundary of non-inferiority, which was set by the company as a difference in ABR of 2.5. The committee acknowledged that the haemophilia B population in the trial was small (n=18) and evidence generation in this group is difficult because haemophilia B is less common than haemophilia A. The committee considered whether the model captured different pathway parameters for haemophilia A and B. It noted that the company's model may not accurately reflect treatment discontinuation because the same discontinuation rate was applied to both haemophilia A and B. At the first meeting, the committee accepted the analyses that included the use of pooled ABR data from people with haemophilia A and B. But it remained concerned that the model had not captured other differences in haemophilia A and B, for example, discontinuation of treatments. The committee requested the company provide further clarity on whether the model captured different treatment pathways and parameters for haemophilia A and B. At consultation, the company stated that the model captured the relevant differences between haemophilia A and B. These included differences between the specific treatments, their costs, dosing frequency and method of administration. The EAG retained the use of pooled ABR estimates but noted that the model has the flexibility to alter baseline bleed rates, dose escalation and bleed relative risks. At the second committee meeting the clinical experts confirmed that although there are different treatment options available for haemophilia A and B, the consequences are the same if either condition is not treated effectively. The committee noted that there are important differences between haemophilia A and

B, including the different comparator costs and dosing estimates, and that these should be used in the modelling. It also noted that most of the effectiveness data comes from people with severe haemophilia A and that the treatment effect in severe haemophilia B is highly uncertain. The committee concluded that a single model using pooled effectiveness estimates for haemophilia A and B was appropriate for decision making. But it noted that the differences between haemophilia A and B for the comparators, including dosing frequencies and method of administration, were sufficient to make separate recommendations for haemophilia A and B.

Health-related quality of life

Bleed-related utility decrements

3.14 In its base case, the company derived differences in quality of life between the 'bleeds' and 'no bleeds' health states through utility decrements applied to acute joint and non-joint bleed events, which only occur in the 'bleeds' state. The company decided it was unfeasible to use EQ-5D scores collected in BASIS because they may not have reflected changes in health-related quality of life related to acute bleed events. The company applied 2 types of utility decrements from the literature dependent upon the type of bleed experienced in the 'bleeds' health state:

- joint bleeds had a utility decrement of 0.28, taken from O'Hara et al. (2018)
- non-joint bleeds had a utility decrement of 0.16, taken from Neufeld et al. (2012).

The company's model assumed these utility decrements applied for 4.5 days. The EAG had concerns about the quality of evidence presented by the company. O'Hara et al. (2018), which was funded by Novo Nordisk, explored the effect of target joints on quality of life in 515 people with severe haemophilia in Europe. The general linear model in the study estimated the effect of the presence of one or more target joints, defined as chronic synovitis. The EAG noted this study was based on target joints and not joint bleeds. It acknowledged these will be linked but the relationship between the

number of joint bleeds and the number of joints with chronic synovitis is unknown. The EAG could not source the utility decrement of 0.28 from O'Hara et al. (2018). Neufeld et al. (2012) surveyed 52 people with haemophilia and all participants had anti-factor antibodies. In this study, participants were asked to complete diary entries and complete an EQ-5D for 90 days or until they had experienced 4 bleeds. The EQ-5D index on non-bleed days was 0.82 and on bleed days was 0.66, yielding a net effect of 0.16. The EAG raised concerns that the Neufeld et al. (2012) study was not limited to non-joint bleeds. The EAG's base case applied the same utility decrement of 0.16 for non-joint bleeds and joint bleeds, obtained from Neufeld et al. (2012), because this study encompassed both types of bleed. The EAG applied the 0.16 utility decrement for 2.5 days because this was implied in Neufeld et al. (2012). The committee acknowledged that joint and non-joint bleeds may not have the same decrements, but they had not been presented with any evidence that measured these together. At the first meeting, the committee acknowledged the concerns raised by the EAG and requested that the company provide further information and justification for using separate joint and non-joint bleed decrements. At consultation, the company updated its base case to align with the EAG's estimates and applied a single utility decrement of 0.16 for a period of 2.5 days. The committee concluded there was uncertainty about the correct values to use for the utility decrements for bleeding events. In the absence of further evidence, it preferred the assumption of a single utility decrement of 0.16 applied for a period of 2.5 days.

Treatment disutility per administration

3.15 The company's model applied treatment administration-related utility decrements. It applied a utility decrement of 0.0003 for each intravenous injection for factor prophylaxis, and a utility decrement of 0.0002 for each subcutaneous injection for marstacimab and emicizumab. These values were taken from Johnston et al. (2021). The EAG noted this study was sponsored by Hoffman-La Roche, the manufacturer of emicizumab, which is administered subcutaneously. The study did a time trade-off by presenting scenarios for 6 health states. The EAG was concerned that the vignettes did not represent factor prophylaxis administration in the NHS because most people self-administer

factor prophylaxis at home. But the vignettes assumed that most factor prophylaxis would be administered in a clinic or hospital. The EAG was also concerned that the disutility estimates for treatment administration were provided at 4 decimal places. So, the actual mean disutility for intravenous administration could be in the range of 0.00025 to 0.00035 and the mean disutility for subcutaneous administration could be in the range of 0.00015 to 0.00025. The EAG noted that because of rounding there may be little to no difference between the 2 central estimates. Also, there were no reported confidence intervals for these values. There is uncertainty whether these confidence intervals would overlap. The EAG's base case provided scenarios for halving utility decrement for treatment administration or applying no utility decrement. The committee was concerned that the time trade-off was capturing not only different treatment administration but also different treatment effects, because the bleeding rates were higher in treatments that had to be administered intravenously. The differences may have been exaggerated. The committee noted these 2 issues were not separated out for each health state. The patient experts stated that they could self-administer factor prophylaxis by intravenous injection quickly but noted that over time it is becoming more difficult to find a vein because scar tissue has formed. The patient experts, in their submission, said that there is a high treatment burden associated with frequent intravenous injections, and that patients and carers value ease of administration and a reduction in treatment burden. The committee concluded that the evidence presented by the company had serious limitations and lacked adequate explanation. But it acknowledged there would be some benefit for a subcutaneous treatment option. At the first meeting the committee requested that the company provide further evidence and modelling for the effect of administration method on health-related quality of life, including a full explanation and justification for the approaches taken. The committee accepted there is likely to be a difference in utility decrements between treatment administration methods, but this remains a source of uncertainty, and the company's approach may have overestimated the benefits of marstacimab.

At consultation, the company presented results from Lu et al. (2024). This is a discrete choice experiment done in the UK, which provided further evidence to support the use of different utility decrements for administration of subcutaneous or intravenous injection. This study reported that changing the method of treatment administration from intravenous injection to subcutaneous injection

was significant. The EAG presented results from a literature review and highlighted a study by Okkels et al. (2024), which was sponsored by Novo Nordisk. This was an online time trade-off study of different treatment administration methods. It reported that there was a utility gain of administering subcutaneous injection compared with intravenous injection and this benefit is similar to those reported by Johnston et al. It also found that there could be additional gains from a prefilled subcutaneous pen, which is the administration method of marstacimab, compared with a single use subcutaneous syringe, which is the administration method of emicizumab. The EAG advised that the methods used in Okkels et al. are superior to those used in Johnston et al. It noted that both studies were done in the general public and not in people with haemophilia. The patient experts explained that as people with haemophilia get older, venous access becomes more difficult and having access to a treatment that has a subcutaneous administration method would be beneficial. The committee noted that Okkels et al. had limitations because this type of study should have been an in-person interview-based study, and a high proportion of data was not used in the final reported results. The committee noted that the utility decrements applied for different methods of treatment administration were the main source of the health gains within the model. It remained concerned about a lack of robust quality-of-life studies in haemophilia. The committee concluded that the treatment administration disutility values provided by Johnston et al. were associated with uncertainty but were appropriate for decision making.

Blended comparator

3.16 The company's base case presented results for haemophilia A and B separately. The haemophilia A comparator treatments were emicizumab and a 'basket' of factor VIII treatments weighted by IQVIA market share. The haemophilia B comparator treatments were a basket of factor IX treatments weighted by IQVIA market share. At the first committee meeting, the EAG preferred to use market share estimates from UKHCDO because they represented real-world usage. The committee was satisfied that combining the factor treatments into baskets of comparators weighted by UKHCDO market share data was appropriate because it reflected real-world UK usage of factor treatments. At consultation, the company submitted a scenario for marstacimab compared with a blended comparator. The

blended comparator combined all the relevant comparators for haemophilia A and B; that is, factor VIII, factor IX and emicizumab. The company considered that this analysis reflects the anticipated opportunity cost of introducing marstacimab to UK clinical practice and provides an alternative way of considering its cost-effectiveness impact. The company noted that because of the large unmet need in haemophilia B for a subcutaneous treatment option, it is expected that more haemophilia B treatments will be displaced by marstacimab compared with haemophilia A treatments. Within this blended comparator analysis, the company weighted the expected uptake of marstacimab across haemophilia A and B. The exact estimates of expected uptake of marstacimab are confidential and cannot be reported here. In the haemophilia A group, the company estimated that 70% of people would have emicizumab. The company noted that this was reported at the UKHCDO annual meeting. The EAG advised that the blended comparator was not appropriate for decision making because of the very different cost-effectiveness estimates between haemophilia A and B. The EAG had previously examined the use of a blended comparator in a scenario and assumed all patients eligible for marstacimab would switch. The EAG used the UKHCDO data on haemophilia A and B prevalence in the UK (83% for haemophilia A and 17% for haemophilia B). For haemophilia A, the EAG noted the annual UKHCDO report stated that the current uptake of emicizumab in people with severe haemophilia A is 59%. The clinical experts confirmed that the greatest uptake of marstacimab would be in haemophilia B. They suggested that the company's estimate of 70% for emicizumab is likely overestimated. The committee noted that NICE's technology appraisal guidance on efanesoctocog alfa for treating and preventing bleeding episodes in haemophilia A considered a blended modelling approach for haemophilia A treatments. But the committee had not been presented with results by the company for a blended haemophilia A comparator. The committee recalled its conclusion that haemophilia A and B are sufficiently distinct to make different recommendations (see section 3.13). It noted that there are important differences in the cost-effectiveness estimates between haemophilia A and B that are affected by the different comparators and their costs, which a blended approach would not capture. The committee concluded that a blended comparator combining all comparator treatments for haemophilia A and B is not suitable for decision making.

Severity

3.17 NICE's methods for conditions with a high degree of severity did not apply to this evaluation.

Cost effectiveness

Acceptable incremental cost-effectiveness ratio

3.18 NICE's manual on health technology evaluations notes that, above a most plausible ICER of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The committee noted the uncertainty in the generalisability of the trial results (see section 3.6), including the small patient numbers for haemophilia B (see section 3.13), bleed-related utility decrements (see section 3.14) and the lack of robust estimates for utility decrements related to treatment administration (see section 3.15). The committee concluded that an acceptable ICER would be towards the lower end of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

Preferred assumptions

3.19 The committee noted its preferred assumptions:

- use UKHCDO data to model treatment effectiveness for baseline ABR for factor prophylaxis and emicizumab (see section 3.9)
- include dose escalation in year 2 (see section 3.10)
- reduce the factor VIII and factor IX prophylaxis doses to 75% of the company's base case (see section 3.12)
- use the pooled clinical-effectiveness estimates for haemophilia A and B (see

section 3.13)

- use a single utility decrement for bleed events of 0.16 applied for a period of 2.5 days (see section 3.14)
- apply treatment administration decrements for intravenous injection and subcutaneous taken from Johnston et al. (see section 3.15)
- present results separately for the different comparators for haemophilia A and B (see section 3.20).

The committee also identified preferred assumptions that aligned with the EAG's base case:

- fix model errors identified by the EAG
- use the UKHCDO data to inform factor VIII and factor IX administration for bleeds to better reflect NHS practice
- cap the emicizumab dose at 100 kg body weight to reflect NHS practice
- assume only 20% of bleeds incur hospital resource use to better reflect clinical practice
- use the UKHCDO data to estimate usage of factor prophylaxis in the basket of comparators for consistency with NHS practice.

Cost-effectiveness estimates

3.20 Because of confidential commercial arrangements for marstacimab, the comparators and other treatments in the model, the exact cost-effectiveness estimates are confidential and cannot be reported here. Using the committee's preferred assumptions, the results showed:

- For haemophilia A, marstacimab was dominated by emicizumab (that is, marstacimab is more expensive and less effective than emicizumab). For the comparison with factor VIII treatments (basket of factor VIII treatments weighted by UKHCDO market share), the ICER exceeded £1 million per QALY gained.

- For haemophilia B, marstacimab dominated factor IX treatments (basket of factor IX treatments weighted by UKHCDO market share); that is, marstacimab is less expensive and more effective than factor IX.

  For people with severe haemophilia A, the cost-effectiveness evidence for marstacimab compared with emicizumab and factor VIII prophylaxis showed that marstacimab is not a cost-effective option in this group. So, the committee concluded that marstacimab could not yet be recommended for routine use for treating severe haemophilia A in people 12 years and older based on the currently available commercial arrangement.

  For people with severe haemophilia B, the cost-effectiveness evidence for marstacimab compared with factor IX showed that marstacimab is a cost-effective option. So, the committee concluded that marstacimab could be recommended for routine use for treating severe haemophilia B in people 12 years and older.

Equality

3.21 The committee noted that a recommendation in severe haemophilia A or B would not be affected by biological sex. Stakeholders advised that some of the treatments for haemophilia A are derived from human blood or human or animal cells. This may not be considered acceptable by people with some religious beliefs. In haemophilia A, the committee noted there are several treatment options. These include emicizumab, which is not derived from human blood products. The committee did not identify this as an equalities issue that would affect its recommendations. Stakeholders and clinical experts explained that some people may have difficulty self-administering an intravenous factor treatment if they have joint damage or a separate disability in addition to haemophilia. The committee noted for haemophilia A there are alternative treatments to intravenous administration, such as emicizumab. The committee concluded that all equalities issues for marstacimab had been considered in its decision making.

Uncaptured benefits

3.22 At the second committee meeting, the company stated that the availability of a subcutaneous treatment option in severe haemophilia A and B would have a positive impact on family members and caregivers because of a reduced burden of administering treatment. The EAG noted that most adults with severe haemophilia A and B self-administer treatment, and children are trained to self-administer from a young age. The clinical expert confirmed that by 12 years of age most people can self-administer but noted this was usually under the supervision of a parent or carer. A patient expert stated there would be an uncaptured benefit of a subcutaneous treatment for older people who may need assistance, including people in care homes. At the second meeting, the committee noted that the benefits of treatment administration had already been captured in the modelling. So, the committee concluded that all the benefits of marstacimab had already been taken into account.

Conclusion

Recommendation

3.23 For severe haemophilia A, the committee concluded that the cost-effectiveness evidence showed that marstacimab at its current price is not a cost-effective use of NHS resources compared with emicizumab and factor VIII prophylaxis. So, marstacimab was not recommended for treating severe haemophilia A in people 12 years and older. For severe haemophilia B, the committee concluded that the cost-effectiveness evidence showed that marstacimab is a cost-effective use of NHS resources compared with factor IX. So, it recommended marstacimab for routine use in severe haemophilia B in people 12 years and older.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days of its date of publication.

4.2 Section 4f of The Innovative Medicines Fund Principles states that a discretionary source of early funding (from the overall Innovative Medicines Fund budget) is available for certain medicines recommended by NICE. In this instance, interim funding has been agreed for marstacimab. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has severe haemophilia B and the healthcare professional responsible for their care thinks that marstacimab is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D. Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation. The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Raju Reddy
Chair, technology appraisal committee D

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager and an associate director.

Alice Pritchard
Technical lead

Victoria Kelly
Technical adviser

Greg O'Toole
Project manager

Ian Watson
Associate director

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