Emicizumab

Essential medicine status

Section: 10. Medicines affecting the blood > 10.2. Medicines affecting coagulation

EMLc | ATC codes: B02BX06

Indication	Haemophilia A ICD11 code: 3B10.0
INN	Emicizumab
Medicine type	Biological agent
List type	Core (EML) (EMLc)
Formulations	Parenteral > General injections > SC: 12 mg per 0.4 mL in vial (EMLc) ; 30 mg per mL in mL vial (EMLc) ; 60 mg per 0.4 mL in vial ; 105 mg per 0.7 mL in vial (EML) ; 150 mg per mL in vial (EML) ; 300 mg per 2 mL in vial (EML)
EML status history	First added in 2025 (TRS 1064)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Main patent is active in several jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Tags	Biological
Wikipedia	Emicizumab
DrugBank	Emicizumab

Expert Committee recommendation

The Expert Committee acknowledged that the established standard of care for people with haemophilia A involves routine prophylaxis with plasma-derived or recombinant coagulation factor VIII (FVIII), or non-factor replacement therapy with emicizumab. Periodic, on-demand treatment with coagulation factors is used in situations of acute bleeds, in people with non-severe disease and for people with severe disease in low-income settings when prophylactic options are unavailable or unaffordable. The Committee noted that among people with haemophilia A receiving prophylaxis with FVIII replacement, about 30% develop inhibitors against FVIII, rendering further FVIII replacement ineffective. Inhibitor development is associated with increased morbidity and mortality. The Committee considered that the systematic review, clinical trial and real-world evidence presented in the application supported the efficacy and safety of emicizumab as prophylactic treatment for adults and children with haemophilia A, both with and without FVIII inhibitors. Compared with no prophylaxis, and prophylaxis with FVIII or bypassing agents, emicizumab was demonstrated to provide meaningful reductions in bleeding rates and the use of bypassing agents, increases in the chance of being bleed-free, maintenance of joint function, reductions in surgical risks and caregiver burden, and improvements in health-related quality of life measurement scores. Most adverse effects were generally mild to moderate, and manageable. Serious thrombotic adverse events have been reported in some trials, associated with concomitant use of emicizumab and activated prothrombin complex concentrate. Overall, the Committee considered that the balance of benefits to harms of emicizumab for people with haemophilia A, with and without FVIII inhibitors was favourable. The Committee noted that multiple economic and budget impact analyses have reported emicizumab prophylaxis to be dominant and/or cost-saving compared with bypassing agents as prophylaxis or as on-demand use in people with haemophilia A and inhibitors. In people with haemophilia A without inhibitors,

economic analyses produced varying cost–effectiveness findings. Nevertheless, the Committee noted that emicizumab has a high price, with prices varying across countries. The Committee noted that strategies to reduce the cost of emicizumab treatment, such as vial sharing and dose/dose interval modifications, are being successfully used in some settings to reduce the budget impact safeguarding the benefits. The Committee noted that emicizumab has wide global regulatory approval for treatment of adults and children with haemophilia A with inhibitors, and for adults and children with severe haemophilia A without inhibitors. Biosimilars are not currently available. The Committee noted and appreciated the contributions submitted during the public consultation process for the application, indicating broad support for the proposal to include emicizumab on the Model Lists. Based on these considerations, the Expert Committee recommended the inclusion of emicizumab to the core list of the EML and EMLc for prophylactic treatment in people with haemophilia A with and without FVIII inhibitors. Further to this recommendation, and in recognition of the current high price of emicizumab, the Committee highlighted that the value of emicizumab prophylaxis is greatest in people with haemophilia A with FVIII inhibitors, in whom factor replacement is ineffective. In people with severe haemophilia A without FVIII inhibitors, prophylaxis with plasma-derived or recombinant FVIII may represent a better value and more affordable treatment option. In considering inclusion of emicizumab on national EMLs in resource-constrained settings, and in line with national needs, decision-makers may wish to prioritize/limit selection and use of emicizumab in the first instance to the population of people with haemophilia A with FVIII inhibitors. They may extend selection and use for people with severe haemophilia A without inhibitors when the price of emicizumab is lower and/or if resources allow.

Background

Emicizumab has not previously been evaluated for inclusion on the Model Lists for treatment of people with haemophilia A. The Model Lists currently include plasma-derived FVIII and desmopressin for use in the treatment of haemophilia A. Pathogen-reduced cryoprecipitate (with non-pathogen-reduced cryoprecipitate as a therapeutic alternative) is also listed for use in the treatment of haemophilia A as an alternative to FVIII in circumstances when plasma-derived clotting factors are not available or affordable.

Public health relevance

The public health relevance of treatments for haemophilia A is well established. The prevalence at birth per 100 000 males is estimated to be 24.6 cases for all severities of haemophilia A, 9.5 cases for severe haemophilia A, 5.0 cases for all severities of haemophilia B, and 1.5 cases for severe haemophilia B (1). According to estimates on the prevalence at birth and based on the world population in 2024, the expected number of people born with haemophilia is about 1.2 million, including 451 000 with severe disease. The prevalence of haemophilia at birth is similar worldwide; however, survival to adulthood, especially in patients with severe disease, is lower in low- and middle-income countries with restricted access to efficacious coagulation therapies (1). Patients treated with exogenous factor VIII replacement can develop inhibitors (alloantibodies) against FVIII, rendering it ineffective. New FVIII inhibitors occur in approximately 30% of people with haemophilia A who receive coagulation factor concentrates. Most patients develop an inhibitor within a median of 9–12 exposure days to FVIII. The overall inhibitor prevalence is reported to be 5–7% (all patients, all severities), but is higher in patients with severe disease (12–13%) (2).

Benefits

Systematic reviews and meta-analyses Non-clotting factor therapies to prevent bleeds in people with congenital haemophilia A or B A 2024 Cochrane systematic review of six randomized controlled trials (397 males aged 12–75 years) evaluated non-clotting factor therapies (concizumab, emicizumab and fitusiran) versus clotting factor therapies, bypassing agents, placebo or no treatment in the prevention of bleeding and bleeding-related complications in people with congenital haemophilia A or B (3). For the comparison of emicizumab prophylaxis (3 mg/kg weekly for 4 weeks followed by 1.5 mg/kg weekly) versus on-demand therapy in people with inhibitors, the review found moderate-certainty evidence from one trial (HAVEN 1, 53 participants) that emicizumab reduced annualized bleeding rates for all bleeds (mean difference (MD) −22.80, 95% confidence interval (CI) −37.39 to −8.21), all treated bleeds (MD −20.40, 95% CI −35.19 to −5.61) and annualized spontaneous bleeds (MD −15.50, 95% CI −24.06 to −6.94) compared with on-demand therapy. Emicizumab did not significantly reduce annualized joint bleeding rates (MD −5.90, 95% CI −15.42 to 3.62) or annualized target joint bleeding rates (MD −2.90, 95% CI −8.61 to 2.81) compared with on-demand therapy. Emicizumab was associated with a significant increase in the proportion of participants with no bleeds (risk ratio (RR) 11.30, 95% CI 1.66 to 77.30). Quality of life outcomes measured using the Haemophilia Quality of Life Questionnaire for Adults showed low-certainty evidence from one randomized controlled trial (40 participants) of improvements in total score (MD −13.20, 95% CI

−20.84 to −5.56) and physical health score (MD −20.20, 95% CI −32.38 to −8.02) (3). For the comparison of emicizumab 1.5 mg/kg weekly prophylaxis versus on-demand therapy in people without inhibitors (one randomized controlled trial (HAVEN 3), 54 participants), there was moderate-certainty evidence that emicizumab reduced annualized bleeding rates for all bleeds (MD −45.10, 95% CI −63.44 to −26.76), for treated bleeds (MD −36.70, 95% CI −60.53 to −12.87) and annualized joint bleeding rate (MD −25.40, 95% CI −45.23 to −5.57). For the comparison of emicizumab prophylaxis (3 mg/kg bi-weekly) versus on-demand therapy in people without inhibitors (one randomized controlled trial, 53 participants), there was moderate-certainty evidence that emicizumab also reduced annualized bleeding rates for all bleeds (MD −45.00, 95% CI −63.19 to −26.81), for treated bleeds (MD −36.90, 95% CI −60.67 to −13.13) and for annualized joint bleeding rate (MD −25.60, 95% CI −45.40 to −5.80). No differences were seen between emicizumab (either dose) or on-demand therapy for the annualized target joint bleeding rate. There was moderate-certainty evidence that bi-weekly emicizumab reduced the annualized spontaneous joint bleeding rate compared with on-demand therapy (MD −15.30, 95% CI −30.46 to −0.14) (3). Another 2024 systematic review and meta-analysis of five publications (one randomized controlled trial, two non-randomized controlled trials and two cohort studies; 556 participants) compared bleeding endpoints between prophylaxis with emicizumab and bypassing agents (4). The emicizumab treatment regimen investigated was 3 mg/kg weekly for 1 month (all publications) followed by 1.5 mg/kg weekly (four publications). Annualized bleeding rates for treated bleeds was the only common parameter reported in all publications. Results of the meta-analysis for all publications found that emicizumab prophylaxis was associated with a significant reduction in annualized bleeding rates for treated bleeds (standard mean deviation (SMD) −1.58, 95% CI −2.50 to −0.66). The authors highlighted the need to consider these results in the context of small population size and potential risk of bias in the studies. A 2023 systematic review of 11 publications from 10 studies (two randomized controlled trials, three non-randomized trials, five observational studies, 858 participants) evaluated the efficacy/effectiveness and safety of emicizumab prophylaxis compared with prophylaxis with FVIII or bypassing agents in patients with haemophilia A without and with inhibitors (5). In patients without inhibitors, a significant reduction in annualized bleeding rates was observed for emicizumab compared with FVIII prophylaxis (SMD −0.6, 95% CI −1.0 to −0.2; P = 0.0002; seven publications, 208 participants). Subgroup analyses showed significant reductions favouring emicizumab from both interventional (SMD −0.6, 95% CI −1.0 to −0.3; P = 0.0007) and observational (SMD −0.7, 95% CI −1.4 to 0.1; P = 0.07) studies. No significant reduction was observed between treatment groups for annualized bleeding rates for spontaneous treated bleeds or traumatic treated bleeds. The certainty of the evidence for these outcomes was very low. In patients with inhibitors, a significant reduction in annualized bleeding rates was observed for emicizumab compared with FVIII prophylaxis (SMD −1.7, 95% CI −2.4 to −0.9; P < 0.00001; seven publications, 97 participants). Subgroup analyses showed significant reductions favouring emicizumab from both interventional (SMD −1.6, 95% CI −3.0 to −0.1; P = 0.03) and observational (SMD −1.9, 95% CI −2.5 to −1.3; P < 0.00001) studies. The certainty of the evidence for these outcomes was very low. The review was not able to measure the effect estimates for annualized bleeding rates for spontaneous or traumatic treated bleeds (5). Randomized and non-randomized trials Studies in people with haemophilia A of any age or severity and with inhibitors to FVIII The HAVEN 1 trial was a phase III, open-label, multicentre, randomized trial that compared emicizumab prophylaxis with no prophylaxis in 109 patients with haemophilia A with inhibitors aged 12 years and older (6). Participants were randomized in a 2:1 ratio to receive emicizumab 3 mg/kg weekly for 4 weeks, followed by 1.5 mg/kg weekly (group A, 35 participants), or no prophylaxis (group B, 18 participants). Participants who had previously received prophylactic treatment with bypassing agents received emicizumab prophylaxis in group C (49 participants). The primary endpoint was difference in the annualized bleeding rates at 24 weeks between treatment groups A and B. The reported annualized bleeding rates were 2.9 events (95% CI 1.7 to 5.0) for emicizumab compared with 23.3 events (95% CI 12.3 to 43.9) for no prophylaxis, representing an 87% difference that significantly favoured emicizumab (risk ratio (RR 0.13; P < 0.001). Zero bleeding events were reported in 22/35 (63%) and 1/18 (6%) of patients randomized to receive emicizumab and no prophylaxis, respectively. Significant differences in favour of emicizumab prophylaxis were also observed in all secondary bleeding-related endpoints. Among the 24 participants who had previously received prophylactic treatment with bypassing agents, emicizumab prophylaxis resulted in a 79% reduction in annualized bleeding rates (P < 0.001). Health related quality of life outcomes from HAVEN 1 were reported in a subsequent study (7). At week 25, significant differences were seen favouring emicizumab in adjusted mean scores on the Haemophilia Quality of Life Questionnaire for Adults (14.0, 95% CI 5.6 to 22.5; P = 0.002) and physical health (21.6, 95% CI 7.9 to 35.2; P = 0.003). The mean proportions of missed work days and days hospitalized were lower in patients treated with emicizumab compared with those who received no prophylaxis. The HAVEN 2 trial was a phase III, open-label non-randomized trial that investigated emicizumab prophylaxis in children aged < 12 years (85 participants) and ≥ 12 years (three participants) with haemophilia A with inhibitors (8). Participants received emicizumab: 1.5 mg/kg weekly (group A, 65 participants), 3 mg/kg bi-weekly every 2 weeks (group B, 10 participants) or 6 mg/kg 4-weekly (group C, 10 participants). The annualized

bleeding rates for treated bleeds for groups A, B and C were 0.3 (95% CI 0.17 to 0.50), 0.2 (95% CI 0.03 to 1.72) and 2.2 (95% CI 0.69 to 6.81), respectively. The proportions of patients experiencing zero bleeds were 77% (group A), 90% (group B) and 60% (group C). An intraindividual comparison of 15 participants who previously took bypassing agent prophylaxis showed that emicizumab prophylaxis reduced the annualized bleeding rates by 99% (95% CI 97.4 to 99.4). Health-related outcomes from HAVEN 2 were reported in a subsequent study (9). Health-related quality of life was assessed using the Haemophilia-Specific Quality of Life Index (Haemo-QoL SF) in 11 children and the Adapted Inhibitor-specific Quality of Life in caregivers. Mean baseline scores across most of the domains on both measures indicated functional impairments. Over the study period (25 weeks), mean scores for physical health or other domains reported by children or caregivers did not change substantially. The HAVEN 4 trial was a phase III, multicentre, non-randomized, open-label, two-stage trial that investigated the efficacy, safety and pharmacokinetics of emicizumab 6 mg/kg 4-weekly for 24 weeks in 41 adults and adolescents with haemophilia A with (n = 5) and without (n = 36) inhibitors (10). The efficacy endpoint was adequate bleed prevention reported as annualized bleed rates for treated bleeds, all bleeds, treated spontaneous bleeds, treated joint bleeds and treated target joint bleeds. Health-related quality of life was evaluated using the Haemophilia Quality of Life Questionnaire for Adults and Haemo-QoL-SF. The annualized bleeding rates for treated bleeds was 2.4 (95% CI 1.4 to 4.3). No treated bleeds were reported in 23/41 participants, while 37/41 participants reported zero to three treated bleeds. The annualized bleeding rates were 4.5 (95% CI 3.1 to 6.6) for all bleeds, 0.6 (95% CI 0.3 to 1.5) for treated spontaneous bleeds, 1.7 (0.8 to 3.7) for treated joint bleeds, and 1.0 (95% CI 0.3 to 3.3) for treated target joint bleeds. Improvements in the Haemophilia Quality of Life Questionnaire for Adults Physical Health Score from baseline to week 25 were also reported. The STASEY trial was a phase IIIb, multicentre single-arm study that evaluated long-term efficacy and safety of emicizumab 3 mg/kg weekly for 4 weeks followed by 1.5 mg/kg weekly in 195 patients aged 12 years and older with haemophilia A with inhibitors (11). The annualized bleeding rate for treated bleeds was 0.5 (95% CI 0.27 to 0.89) with 82.6% of participants experiencing zero treated bleeds. The annualized bleeding rates for all bleeds was 1.1 (95% CI 0.80 to 1.47), with 64.9% of patients experiencing zero bleeds. A 2023 post-marketing study in the United Kingdom evaluated bleeding outcomes in patients with haemophilia A with inhibitors using data for 117 patients from a national registry and patient-reported Haemtrack data over 3 years (January 2018 to September 2021) (12). Of the 117 patients, 106 had severe haemophilia and 11 had non-severe disease. Four patients were younger than 2 years. Over a mean emicizumab treatment duration of 42 months, the mean annualized bleeding rate was 0.32 events (95% CI 0.18 to 0.39). A within-person comparison of 74 patients showed an 89% reduction in annualized bleeding rates after switching to emicizumab (from no treatment, plasma-derived or recombinant FVIII, activated prothrombin complex concentrate or multiple treatments) and an increase in the zero-treated bleed rate from 45% to 88% ($P < 0.01$). In a subgroup of 37 patients who switched from other treatments to emicizumab, over a median 25 months of follow-up, total haemophilia joint health scores improved from baseline in 39% of patients, remained stable in 36% and deteriorated in 25%. The within-person change in total haemophilia joint health scores was statistically significant but did not meet the threshold for clinical significance. Studies in people with severe haemophilia A without inhibitors to FVIII The HAVEN 3 trial was an open-label, multicentre randomized trial that evaluated emicizumab prophylaxis in 152 participants aged 12 years or older with severe haemophilia A without inhibitors (13). Participants were randomized in a 2:2:1 ratio to receive emicizumab 1.5 mg/kg weekly (group A, n = 36), emicizumab 3 mg/kg bi-weekly (group B, n = 35) or no prophylaxis (group C, n = 18). Participants who had previously been receiving FVIII prophylaxis were given emicizumab 1.5 mg/kg weekly (group D, n = 63). The primary endpoint was the difference in the rate of treated bleeding events over a period of at least 24 weeks between treatment groups. The annualized bleeding rates were 1.5 (95% CI 0.9 to 2.5), 1.3 (95% CI 0.8 to 2.3) and 38.2 (95% CI 22.9 to 63.8) in groups A, B and C, respectively. Compared with group C, the bleeding rates were significantly lower in both group A (rate ratio (RR) 0.04, 95% CI 0.02 to 0.08; $P < 0.001$) and group B (RR 0.03, 95% CI 0.02 to 0.07; $P < 0.001$). The percentages of participants with zero bleeding events was 56% (95% CI 38% to 72%) in group A, 60% (95% CI 42% to 76%) in group B, and 0% (95% CI 0% to 18%) in group C. Intraindividual comparison of 48 participants in group D showed a significantly lower annualized bleeding rate favouring emicizumab over FVIII prophylaxis (RR 0.32, 95% CI 0.20 to 0.51; $P < 0.001$). A 2022 study evaluated the effect of emicizumab prophylaxis on bone/joint health in 151 participants with haemophilia A without inhibitors from the HAVEN 3 study (14). Haemophilia joint health scores were evaluated at baseline and weeks 49 and 97 in patients receiving emicizumab (n = 134), and at baseline and weeks 49, 73 and 97 in patients who switched to emicizumab after 24 weeks of no prophylaxis (n = 17). At week 49, the mean improvement in total haemophilia joint health score from baseline for all participants was −1.86 (95% CI −3.53 to −0.20). Among participants with at least one target joint at study entry (n = 71), the mean improvement in haemophilia joint health total score at week 49 was −2.28 (95% CI −4.15 to −0.42) and the mean improvement in the haemophilia joint health score joint-specific domain was −2.13 (95% CI −3.96 to −0.29). Changes from baseline were maintained through week 97 in this patient group. In

participants aged 12–39 years (n = 67) regardless of target joint status or previous treatment regimen, the mean improvement in haemophilia joint health total score was −3.22 (95% CI−5.40 to −1.04) and the mean improvement in haemophilia joint health score joint-specific domain was −3.04 (95% CI −5.12 to −0.97). Changes from baseline were maintained through week 97 in this patient group. A change of ≥ 4 for total haemophilia joint health scores and of ≥ 2 for haemophilia joint health score joint-specific domain is considered clinically relevant. A 2024 study evaluated the long-term outcomes of emicizumab in 191 patients with haemophilia A without inhibitors from the HAVEN 3 and HAVEN 4 studies (15). Across the two studies, the median duration of emicizumab exposure was 248.1 weeks (range 6.1–287.1 weeks). The mean annualized bleeding rates for treated bleeds were 2.0 (95% CI 0.23 to 7.15) for weeks 1 to 24 and 0.9 (95% CI 0.01 to 5.28) by weeks 217 to 240. The HAVEN 5 trial was a phase III, open-label, randomized study of emicizumab in 70 participants with severe haemophilia A without inhibitors across the Asia-Pacific region (China, Malaysia and Thailand) (16). Participants were randomized in a 2:2:1 ratio to receive emicizumab 1.5 mg/kg weekly (group A, n = 29), emicizumab 6 mg/kg 4-weekly (group B, n = 27) or no prophylaxis (group C, n = 14). For the primary efficacy endpoint of annualized bleeding rates, after at least 24 weeks of study treatment, the annualized bleeding rates were 1.0 (95% CI 0.53 to 1.85), 1.0 (95% CI 0.50 to 1.84) and 27.0 (95% CI 13.29 to 54.91) in groups A, B and C, respectively. Significant reductions in annualized bleeding rates were observed for both emicizumab-treatment groups compared to no prophylaxis (RR 0.04; P < 0.0001). Other studies in people with haemophilia A with and without inhibitors to FVIII The HAVEN 7 trial is an ongoing phase IIIb, multicentre, open label, single-arm trial of emicizumab prophylaxis 3 mg/kg/week for 4 weeks followed by 3 mg/kg bi-weekly for 52 weeks, followed by long-term follow-up in 55 male infants aged ≤ 12 months with severe haemophilia A without inhibitors (17). Following a median duration of 101.9 weeks, the reported annualized bleeding rates were 2.0 (95% CI 1.49 to 2.66) for all bleeds, 0.4 (95% CI, 0.30 to 0.63) for treated bleeds, 0.0 (95% CI, 0.01 to 0.09) for treated joint bleeds and 0.1 (95% CI, 0.02 to 0.12) for treated muscle bleeds. Zero-treated bleeds were reported in 54.5% of participants. A total of 207 bleeds were reported in 46 patients, most of which (87.9%) were traumatic. A 2021 study evaluated long-term efficacy outcomes of emicizumab prophylaxis in 400 patients with haemophilia A with or without inhibitors using pooled data from long-term follow-up of the HAVEN 1-4 trials (18). Across a median efficacy period of 120.4 weeks, the annualized bleeding rates for treated bleeds was 1.4 (95% CI 1.1 to 1.7) and for all bleeds was 2.6 (95% CI 2.2 to 3.1). In an analysis of 24-week treatment intervals, annualized bleeding rates for treated bleeds declined from 1.9 (95% CI 0.2 to 7.1) for weeks 1–24 (n = 391) to 0.8 (95% CI 0.0 to 5.2) for weeks 25–48 (n = 374), then remained stable to weeks 121–144 (0.4, 95% CI 0.0 to 5.0). The proportion of participants with zero bleeds increased from 70.8% for weeks 1–24 to 82.4% for weeks 121–144. The proportion of participants with three or fewer treated bleeds and no treated target joint bleeds at weeks 121–144 were 97.6% and 94.1%, respectively. A 2022 study investigated surgical outcomes in people with haemophilia A with and without inhibitors receiving emicizumab prophylaxis using pooled data from the HAVEN 1–4 trials (19). A total of 233 surgeries (215 minor, 18 major) were carried out during these trials. The median emicizumab exposure before surgery was 278.0 days (interquartile range (IQR) 177.0 to 431.0 days). About two thirds (141/215, 65.6%) of the minor surgeries were managed without additional prophylactic factor concentrate, with most of these (121/141, 85.8%) not associated with a postoperative bleed. Of the major surgeries, most (15/18, 83.3%) were managed with additional prophylactic factor concentrate, with most (12/15, 80.0%) not associated with intraoperative or postoperative bleeds. A 2021 prospective study of longitudinal real-world data evaluated the efficacy and safety of emicizumab prophylaxis in 107 patients (including 58 children) with severe haemophilia A with and without inhibitors (20). Participants were followed for a median of 67 weeks. Zero bleeds were reported in 53/107 (49.5%) participants. A 2024 study evaluated data from the multicentre, prospective observational PedNet Registry for children with haemophilia A and ≥ 50 FVIII exposures or inhibitors receiving prophylactic emicizumab (21). A total of 177 patients started emicizumab at a median of 8.6 years (IQR 4.8 to 13.1 years); 64% had no FVIII inhibitors. The follow-up period before emicizumab was 1.7 years (IQR 1.2 to 1.9 years) and during prophylaxis with emicizumab was 1.3 years (IQR 0.9 to 2.1 years). In participants without inhibitors, the mean annualized bleeding rate was significantly reduced after starting emicizumab from 2.41 to 1.11 (incidence rate ratio (IRR) 0.47, 95% CI 0.35 to 0.63; P < 0.001), as was the mean annualized joint bleeding rate from 0.74 to 0.31 (IRR 0.43, 95% CI 0.26 to 0.69; P < 0.001). In participants with inhibitors, reductions in the annualized bleeding rates were greater: mean annualized bleeding rate reduced from 5.08 to 0.75 (IRR 0.15, 95% CI 0.10 to 0.21; P < 0.001) and mean annualized bleeding joint rate reduced from 1.90 to 0.34 (IRR 0.17, 95% CI 0.10 to 0.28; P < 0.001) A prospective study in Côte d'Ivoire evaluated the effect of emicizumab prophylaxis on bleeds, clotting factor concentrate consumption, quality of life and patient/parent satisfaction in 33 boys (2–13 years) with severe haemophilia A with and without inhibitors (22). In this setting, access to clotting factor concentrates is limited to humanitarian aid. Twelve months after initiation of emicizumab, significant reductions were reported in mean (standard error) annualized bleeding rate (−7.3 (0.8); P < 0.0001) and annualized spontaneous joint bleeding rate (−3.3 (0.6); P < 0.0001). The proportion of boys with no spontaneous joint bleeds increased from 18% to 100%.

Three boys (without inhibitors) required a single FVIII infusion following a traumatic bleed. At 6 months, health-related quality of life measures significantly improved and perception of treatment efficacy was positively rated by children and parents.

Harms

From the 2024 Cochrane systematic review, there was moderate-certainty evidence that emicizumab prophylaxis probably increased total adverse events compared with on-demand therapy in people with inhibitors (RR 1.97, 95% CI 1.26 to 3.10; one randomized controlled trial (HAVEN 1), 52 participants). No significant difference was seen between treatment groups for serious adverse events (RR 1.32, 95% CI 0.48 to 3.63). There was moderate-certainty evidence that other adverse events occurred more frequently with emicizumab prophylaxis compared with on-demand therapy (RR 1.94, 95% CI 1.22 to 3.09), with the most frequently reported adverse events being injection-site reactions (24%), upper respiratory tract infections (21%), fatigue (9%), headache (9%) and arthralgia (6%). For people without inhibitors, there was moderate-certainty evidence that emicizumab prophylaxis (either dose) was associated with more adverse events (1.5 mg/kg weekly: RR 2.83, 95% CI 1.47 to 5.47; 3 mg/kg bi-weekly: RR 1.71, 95% CI 1.06 to 2.77). No differences were seen between emicizumab (either dose) or on-demand therapy for serious adverse events. Other adverse events occurred more frequently with emicizumab (1.5 mg/kg weekly: RR 3.50, 95% CI 1.66 to 7.39; 3.0 mg/kg bi-weekly: RR 3.39, 95% CI 1.60 to 7.18). The most commonly reported adverse events with emicizumab 1.5 mg/kg weekly and 3 mg/kg twice a week were injection-site reactions (25% and 20%), upper respiratory tract infections (both 11%), nasopharyngitis (6% and 17%), arthralgia (19% and 17%), headache (8% and 11%) and influenza (3% and 9%) (3). In the HAVEN 1 trial, 198 adverse events were reported in 103 participants receiving emicizumab. All but one were of mild intensity and resolved. Events occurring in at least 5% of participants were injection-site reactions (15%), headache (12%), upper respiratory tract infection (9%), fatigue and arthralgia (both 6%). Twelve serious adverse events occurred in nine participants including thrombotic microangiopathy and thromboembolism in two participants each who had received multiple infusions of activated prothrombin complex concentrate while receiving emicizumab prophylaxis before event onset (6). These thrombotic events led to the United States Food and Drug Administration including a boxed warning in the emicizumab product label about concomitant use of emicizumab and activated prothrombin complex concentrate. In the HAVEN 2 trial, 712 adverse events were reported in 82 participants receiving emicizumab. All were non-serious and resolved without treatment. Twenty-one serious adverse events were reported, with only a single report of development of anti-drug antibodies being assessed by trial investigators as being treatment related. The most common adverse events were nasopharyngitis (27.5%) and injection-site reactions (30.7%). No thromboembolic events were reported (8). In the HAVEN 4 trial, 148 adverse events were reported in 30 participants receiving emicizumab, of which only one was serious (rhabdomyolysis) and considered unrelated to treatment. The most common adverse events deemed to be treatment-related were injection-site reactions (22%), chills, pre-syncope, erythema, and rash (2% each). No thrombotic events were reported. Two participants developed anti-drug antibodies (10). The STASEY trial assessed the safety of emicizumab prophylaxis as the primary endpoint. The median duration of exposure to emicizumab for the evaluable population (n = 193) was 103.1 weeks. A total of 800 adverse events were reported in 163 participants. The most frequently reported adverse events occurring in ≥ 5% of participants receiving emicizumab were arthralgia (17.1%), nasopharyngitis (15.5%), and headache (15.0%). Injection-site reactions were reported in 11.4% of participants, with most assessed as being treatment related. Fifty serious adverse events were reported in 31 participants, but only one was considered to be treatment related (a catheter-site abscess) which resolved with treatment. No study participants experienced a thrombotic microangiopathy. Thrombotic events reported in two participants were considered unrelated to treatment (11). In the HAVEN 3 trial, 543 adverse events were reported in 127 participants. The most common adverse events reported in ≥ 5% of participants were injection-site reactions (25%), arthralgia (19%) and nasopharyngitis (12%). Fourteen serious adverse events were reported, but none were considered to be related to treatment. No deaths, thrombotic microangiopathy or thromboembolic events were reported (13). In the HAVEN 5 trial, 185 adverse events were reported in 44 participants, the majority of which were grade 1 or 2. The most commonly reported adverse events were upper respiratory tract infection (27.1%) and injection-site reactions (12.9%). No deaths, thrombotic microangiopathy, or thromboembolic events were reported. Treatment-induced anti-drug antibodies were detected in 12.5% of evaluable participants, including one with neutralizing potential (16). In the HAVEN 7 trial in infants, at the time of primary analysis, no intracranial haemorrhage events had occurred, no adverse events led to study discontinuation or treatment changes, and no new safety signals were identified. A total of 631 adverse events were reported in 55 participants. All treatment-related adverse events were grade 1 injection-site reactions. No thrombotic microangiopathy or thromboembolic events were reported (17). A 2021 study evaluated the development of anti-emicizumab antibodies in people with haemophilia A receiving emicizumab, pooling data from the HAVEN 1-5, HOHOEMI and STASEY studies) (23). The study evaluated immunogenicity data for 668 participants

(98 children aged < 12 years and 570 adolescents and adults aged ≥ 12 years). All participants were male and had a median age of 28 years. Most participants (62.1%) had FVIII inhibitors at baseline. Median emicizumab exposure was of 103.1 weeks (IQR 82.4 to 148.1). Results showed that 34 participants (5.1%) developed anti-drug antibodies after exposure to emicizumab. Incidence was similar in children and adolescents/adults. In 14/34 (41.2%) participants, anti-drug antibodies were transient, detected only at a single time point. Among the remaining 20 participants with anti-drug antibodies, 15 (75.0%) had no detectable antibodies at the last time point assessed, after a median duration of positivity for anti-drug antibodies of 20 weeks. In vitro analysis showed that anti-drug antibodies were neutralizing in 18/34 cases (52.9%) and associated with decreased emicizumab concentration in 4/34 (11.8%) participants, one of whom discontinued emicizumab due to loss of efficacy.

Cost / cost effectiveness

Studies in people with haemophilia A with inhibitors The application presented the findings from budget impact, cost–utility and cost–effectiveness studies identified through a literature search. Various studies from Brazil (25), Canada (26), France (27), India (28), Iran (Islamic Republic of) (29), Italy (30), Malaysia (31), Peru (32), Republic of Korea (33), Spain (34), South Africa (35) and United States of America (36) report emicizumab prophylaxis to be dominant and/or associated with cost-savings compared with bypassing agents as prophylaxis or as on-demand use in people with haemophilia A and inhibitors. Summaries of the findings were presented in the application. Studies in people with haemophilia A without inhibitors Evidence from economic studies of cost savings and cost–effectiveness of emicizumab show more variability for the treatment of people with severe haemophilia A without inhibitors. Studies show cost savings and cost–effectiveness with emicizumab compared to FVIII in India and the United States, but not in Europe and the United Kingdom of Great Britain and Northern Ireland. A study in India evaluated the cost–effectiveness of emicizumab prophylaxis compared to on-demand therapy, and low-, intermediate-, and high-dose prophylaxis with FVIII in people with haemophilia A without inhibitors (37). In the base-case analysis, emicizumab was cost-effective compared with high-dose prophylaxis, with an incremental cost–effectiveness ratio of 27 869 Indian rupees (INR) per quality adjusted life year (QALY). Compared with on-demand therapy, intermediate-dose prophylaxis and low-dose prophylaxis, emicizumab prophylaxis was not shown to be cost-effective at a willingness-to-pay threshold of 1 x per capita gross domestic product with incremental cost–effectiveness ratios of INR 255 876, INR 264 592 and INR 305 398 per QALY, respectively. Emicizumab could be considered cost-effective compared with on-demand therapy, and low- and intermediate-dose prophylaxis if the willingness-to-pay threshold is greater than 1 x per capita gross domestic product. One-way sensitivity analysis highlighted emicizumab cost as the parameter with the greatest impact on incremental cost–effectiveness ratios. An economic model study (funded by Genentech) estimated short- and long-term clinical and economic outcomes of emicizumab prophylaxis versus short-acting recombinant FVIII prophylaxis in people with haemophilia A without inhibitors from United States payer and societal perspectives (38). Over a lifetime horizon, the cumulative number of all treated bleeds and joint bleeds avoided on emicizumab versus recombinant FVIII prophylaxis were 278.2 and 151.7, respectively. Arthropathy and development of FVIII inhibitors were delayed. Total direct and indirect costs were lower for emicizumab versus recombinant FVIII prophylaxis for all modelled time horizons (97 159 United States dollars (US$) versus US$ 331 610 at 1 year, US$ 603,146 versus US$ 1 459 496 at 5 years and US$ 15 238 072 versus US$ 22 820 281 over a lifetime horizon). Sensitivity analyses showed that clinical outcomes were sensitive to efficacy inputs, while economic outcomes were driven by the discount rate, dosing schedules and treatments after inhibitor development. The results for moderate to severe patients were consistent with findings in the severe population. Compared with short-acting recombinant FVIII, the model found that emicizumab prophylaxis led to superior patient outcomes and cost savings. Another economic study from the United States evaluated the cost–effectiveness of emicizumab versus standard, extended and ultra-extended half-life recombinant FVIII products for prophylaxis in people with severe haemophilia A without inhibitors (39). Over a lifetime time horizon, emicizumab was estimated to be less costly (US$ 17.0 million versus US$ 24.0 million US$ 19.3 million and US$ 18.2 million for ultra-extended, standard and extended half-life recombinant FVIII) and more effective (18.61 QALYs versus 18.58 QALYs, 16.91 QALYs and 17.33 QALYs for ultra-extended, standard and extended half-life recombinant FVIII, respectively). Ultra-extended half-life recombinant FVIII was associated with fewer bleeds than emicizumab over a lifetime (26.58 versus 59.91), while emicizumab was associated with fewer bleeds over a lifetime compared with extended and standard half-life recombinant FVIII (59.91 versus 198.45 and 108.58, respectively). Results were robust to one-way and probabilistic sensitivity analyses. Overall, findings suggested that emicizumab was dominant over a lifetime compared with available recombinant FVIII prophylaxis in the United States of America. Economic studies from Europe and the United Kingdom evaluated the cost–effectiveness of emicizumab compared with extended half-life recombinant FVIII as prophylaxis in people with haemophilia A without inhibitors. A cost-minimization study from the European health-care payer perspective found incremental savings over 5 years for extended half-life recombinant FVIII compared

with emicizumab of 89.3 million euros (€) to €150.0 million in adolescents/adults and from €173.4 million to €253.2 million in children < 12 years. The model included costs for drug acquisition, emicizumab wastage and additional FVIII for breakthrough bleeds. Emicizumab wastage accounted for 6% and 26% of its total cost in adolescents/adults and children, respectively (using manufacturer's recommendations) (40). A cost–effectiveness study from the United Kingdom also compared extended half-life recombinant FVIII and emicizumab as prophylaxis in people with haemophilia A without inhibitors (41). The base-case analysis found that individualized prophylaxis with extended half-life recombinant FVIII was the dominant treatment strategy, with lower costs, more QALYs and fewer bleeds.

WHO guidelines

WHO guidelines for the treatment of haemophilia are not available. World Federation of Hemophilia guidelines for management of haemophilia (24) include the following recommendations in relation to emicizumab. People with haemophilia A with inhibitors • For patients with haemophilia A and inhibitors receiving emicizumab, conduct bovine chromogenic assays to monitor inhibitor levels. • For patients with haemophilia A and inhibitors receiving emicizumab, undertake close clinical monitoring for thrombosis, adverse reactions and thrombotic microangiopathy. • As emicizumab is used to prevent, but not treat, acute bleeds in patients with haemophilia A and inhibitors, clotting factor replacement therapy is recommended for acute bleeds. • For patients with haemophilia A and inhibitors receiving emicizumab who have an acute bleed, clotting factor replacement therapy including FVIII is recommended for patients with low-responding inhibitors; recombinant FVIIa is preferred over activated prothrombin complex concentrates for patients with high-responding FVIII inhibitors due to the risk of thrombotic microangiopathy. • For patients with severe haemophilia A and inhibitors, emicizumab is preferred over bypass agent prophylaxis to reduce bleeding episodes, as emicizumab appears to be superior to bypass prophylaxis. People with severe haemophilia without inhibitors • For patients with haemophilia A or B with a severe phenotype, it is strongly recommended that such patients be on prophylaxis sufficient to prevent bleeds at all times, but that prophylaxis should be individualized, taking into consideration patient bleeding phenotype, joint status, individual pharmacokinetics, and patient self-assessment and preference. • For patients with severe phenotype haemophilia A without inhibitors, prophylaxis with emicizumab will prevent haemarthrosis, and other spontaneous and breakthrough bleeding.

Availability

Emicizumab has regulatory approval for the treatment of children and adults with haemophilia A with inhibitors in 122 countries and without inhibitors in 112 countries. Emicizumab is marketed in over 100 countries with 29 low- to middle-income countries accessing emicizumab through the World Federation of Hemophilia Humanitarian Aid Program (42). Currently, no biosimilars of emicizumab are available.

Other considerations

The Blood and Other Products of Human Origin team within the Department of Health Products, Policy and Standards reviewed and provided comments on the application. The technical team was supportive of the inclusion of emicizumab on the EML and EMLc based on evidence of favourable efficacy and cost-effectiveness.

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