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ADIS DRUG EVALUATION

Emicizumab: A Review in Haemophilia A

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Abstract

Emicizumab (Hemlibra®), a recombinant, humanized, bispecific monoclonal antibody, restores the function of missing activated factor VIII (FVIII) by bridging FIXa and FX to facilitate effective haemostasis in patients with haemophilia A. Subcutaneous emicizumab is approved in several countries, including in the USA and Japan, for the routine prophylaxis of bleeding episodes in patients with haemophilia A with or without FVIII inhibitors. It is also approved in the EU for the routine prophylaxis of bleeding episodes in patients with haemophilia A with inhibitors or severe haemophilia A without inhibitors. In phase III clinical trials, emicizumab prophylaxis significantly reduced annualized bleeding rates compared with no prophylaxis in adolescents and adults with haemophilia A with or without inhibitors, and prevented or substantially reduced bleeding in children with haemophilia A with or without inhibitors. Emicizumab was also associated with beneficial effects on health-related quality of life and health status, and was generally well tolerated. In view of its convenient route of administration and versatile dosage regimens (maintenance dose of once every 1, 2 or 4 weeks), emicizumab provides an effective and generally well-tolerated alternative to conventional FVIII replacement products for the prophylaxis of bleeding episodes in patients with haemophilia A, regardless of the presence or absence of inhibitors.

Emicizumab: clinical considerations in haemophilia A

Mimics the cofactor activity of activated FVIII
Significantly reduces annualized bleeding rates compared with no prophylaxis in adolescents and adults
Prevents or substantially reduces bleeding in children
Generally well tolerated

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1 Introduction

Congenital haemophilia A is an inherited X-linked bleeding disorder caused by a deficiency of coagulation factor VIII (FVIII) [1]. Severe haemophilia A (FVIII level < 1 IU/dL or < 1% of normal) is characterized by spontaneous bleeding episodes, particularly in joints and muscles, usually in the absence of an identifiable haemostatic challenge [1].

Prophylactic FVIII replacement therapy is the standard of care for the management of patients with haemophilia A [2]. However, conventional FVIII preparations have short half-lives (8–12 h), necessitating frequent intravenous infusions (usually 3–4 times per week). Extended half-life FVIII products have been developed by attaching a molecule of recombinant FVIII to a long-lasting molecule such as albumin, polyethylene glycol or the Fc fragment of immunoglobulin (Ig) G. Despite the advantages of these FVIII products (e.g. reduced infusion frequency, improved treatment compliance), they still require intravenous administration and can lead to the development of neutralizing antibodies (inhibitors) against FVIII [2]. The formation of inhibitors is a significant complication of haemophilia A treatment [3]. These antibodies render factor replacement therapy ineffective, thereby increasing the risk of serious bleeding and morbidity [3]. Thus, there is a need for new treatment

options that address the challenges associated with FVIII replacement products.

The first commercially available non-factor replacement product is emicizumab (Hemlibra®), a subcutaneously administered, recombinant, humanized, bispecific monoclonal antibody designed to mimic the cofactor activity of activated FVIII. Emicizumab is approved in several countries, including in the USA and Japan, for the routine prophylaxis of bleeding episodes in patients with haemophilia A with or without FVIII inhibitors [4, 5]. It is also approved in the EU for the routine prophylaxis of bleeding episodes in patients with haemophilia A with inhibitors or severe haemophilia A without inhibitors [6]. This review discusses pharmacological, efficacy and tolerability data relevant to the use of emicizumab in this patient population.

2 Pharmacodynamic Properties of Emicizumab

Emicizumab, a humanized bispecific IgG1 antibody, binds FIX/FIXa and FX/FXa at their respective epidermal growth factor-like domains with micromolar affinities [7]. Emicizumab bridges activated FIX and FX in a manner similar to activated FVIII [7], thereby restoring the function of missing activated FVIII (which is required for effective haemostasis) [4, 6]. The plasma concentration of the antigen-bridging ternary complex (FIX-emicizumab-FX) correlates with the cofactor activity of emicizumab [7]. Because emicizumab has no structural relationship or sequence homology to FVIII, it does not induce or enhance the development of FVIII inhibitors [4, 6].

Emicizumab demonstrated haemostatic activity in animal models of haemophilia A [8–11]. For example, in a long-term primate model of acquired haemophilia A, emicizumab prophylaxis prevented the occurrence of the spontaneous bleeding symptoms that were observed in the control group [10]. In a model of haemophilia A blood, emicizumab increased clot stability in the presence of activated prothrombin complex concentrate (aPCC), which may partially explain the increased risk of thrombotic events when emicizumab and aPCC are used concurrently (Sect. 5) [12].

The activated FVIII-mimetic function of emicizumab was demonstrated in early phase I and phase I/II trials [13–15]. For example, in a first-in-human study in healthy male adults ($n = 64$), emicizumab shortened activated partial thromboplastin time (aPTT) and increased peak height of thrombin generation in a dose-dependent manner [15]. In the pivotal HAVEN 1 trial ($n = 103$ evaluable), emicizumab exhibited concentration-dependent pharmacodynamic effects on thrombin generation and FVIII activity in male patients with haemophilia A [16]. The aPTT was normalized (i.e. < 40 s) after the first dose of emicizumab and remained stable thereafter. When assessed using a FVIII chromogenic activity assay containing human factors, mean FVIII activity increased from < 1% at baseline to approximately 30% during treatment with emicizumab. During emicizumab treatment, there were no significant changes over time in antigen levels of FIX and FX, von Willebrand factor, prothrombin time, D-dimer or prothrombin fragment 1.2 [16].

3 Pharmacokinetic Properties of Emicizumab

Subcutaneous emicizumab demonstrates dose-proportional pharmacokinetics across a dose range of 0.3–6 mg/kg once weekly [4, 6]. When an initial loading dose of emicizumab (1 or 3 mg/kg) was administered in patients with haemophilia A, steady state plasma concentrations were reached after ≈ 12 weeks [14]. Following administration of emicizumab 3 mg/kg once weekly for 4 weeks, mean trough plasma concentrations of 52.6 µg/mL are achieved at week 5 [4, 6]. The mean absorption half-life of emicizumab is 1.6 days and its absolute bioavailability following a 1 mg/kg dose is 80.4–93.1% [4, 6]. The mean apparent volume of distribution (Vd) of emicizumab is 10.4 L. The mean apparent clearance of emicizumab is 0.27 L/day and the mean apparent elimination half-life is ≈ 27 days [4, 6]. Although the metabolism of emicizumab has not been directly studied, the primary route of IgG antibody clearance is via proteolytic catabolism [6].

Emicizumab pharmacokinetics have been analysed in patients with haemophilia A in phase III trials (Sect. 4). The pharmacokinetic profile of emicizumab in patients with haemophilia A without inhibitors in HAVEN 3 was generally consistent with that in patients with haemophilia A with inhibitors in HAVEN 1 [17]. Likewise, the pharmacokinetic profiles of emicizumab administered every 2 weeks (in HAVEN 2 and 3) or every 4 weeks (in HAVEN 2 and 4) were generally consistent with that after once-weekly administration (in HAVEN 1), although mean trough concentrations were lower when emicizumab was administered every 4 weeks versus every 2 weeks [18].

The pharmacokinetics of emicizumab are not impacted by age (1–77 years), race (white, Asian or black), inhibitor status, mild hepatic impairment [total bilirubin 1 x to ≤ 1.5 x upper limit of normal (ULN) and any aspartate aminotransferase (AST) level], moderate hepatic impairment (total bilirubin 1.5 x to ≤ 3 x ULN and any AST level), mild renal impairment [creatinine clearance (CL_{CR}) 60–89 mL/min] or moderate renal impairment (CL_{CR} 30–59 mL/min) [4]. The apparent clearance and Vd of emicizumab increase with increasing bodyweight (9–156 kg); dosing by bodyweight (mg/kg) provides similar exposure to emicizumab across bodyweight range [4].

Drug-drug interaction studies with emicizumab have not been conducted [4, 6]. Based on clinical experience, a drug interaction may exist between emicizumab and aPCC (Sect. 5) [4, 6]. Hypercoagulability may occur when emicizumab is coadministered with recombinant FVIIa or FVIII [6]. The possibility of thrombotic events should be considered when systemic anti-fibrinolytics are coadministered with aPCC or recombinant FVIIa in patients receiving emicizumab [6].

4 Therapeutic Efficacy of Emicizumab

The efficacy of subcutaneous emicizumab for the prophylaxis of bleeding events was evaluated in several open-label, multicentre, phase III trials which enrolled male adults and adolescents (HAVEN 1 [19], HAVEN 3 [20], HAVEN 4 [21], STASEY [22]) or children (HAVEN 2 [23], HOHOEMI [24]) with haemophilia A with [19, 21–23] or without [20, 21, 24] inhibitors. Some patients in the HAVEN trials were rolled over from a global non-interventional study.

4.1 In Adults and Adolescents Aged ≥ 12 Years

Adults and adolescents aged ≥ 12 years were eligible to enter HAVEN 1, 3 or 4 if they had congenital haemophilia A of any severity (HAVEN 1 [19]) or severe congenital haemophilia A (HAVEN 3 and 4 [20, 21]) and had been treated with episodic or prophylactic bypassing agents (HAVEN 1 and 4 [19, 21]) or FVIII products (HAVEN 3 and 4 [20, 21]) for ≥ 24 weeks prior to study entry.

4.1.1 In Patients with Inhibitors

4.1.1.1 HAVEN 1 HAVEN 1 enrolled 109 patients (median age 28 years) with haemophilia A with inhibitors, 94% of whom had severe haemophilia A [19]. Patients who had previously received episodic treatment with bypassing agents were randomized in a 2:1 ratio to receive emicizumab prophylaxis (group A) or no emicizumab prophylaxis (group B). Patients who had previously received prophylactic treatment with bypassing agents were assigned to emicizumab prophylaxis (group C). Group D comprised patients who were previously enrolled in the non-interventional study but were unable to enrol in groups A, B or C before they closed to enrolment. Patients in groups A, C and D received subcutaneous emicizumab prophylaxis (3 mg/kg once weekly for 4 weeks, then 1.5 mg/kg once weekly thereafter). Data from group D were not included in the efficacy analysis due to the short follow-up at the time of data cut-off [19].

Emicizumab prophylaxis significantly reduced the rate of bleeding events compared with no prophylaxis in adults and adolescents aged ≥ 12 years with haemophilia A with inhibitors [19]. For treated bleeds, the annualized bleeding rate over a period of ≥ 24 weeks was significantly reduced with emicizumab prophylaxis compared with no prophylaxis (primary endpoint; Table 1). Results were generally consistent across all subgroups regardless of age, race, bleeding rate in the 24 weeks prior to study entry, and presence of target joints. The annualized rates of all bleeds, treated spontaneous bleeds, treated joint bleeds and treated target joint bleeds were significantly reduced with emicizumab prophylaxis compared with no prophylaxis (Table 1) [19]. Annualized bleeding rates for all bleed types favoured emicizumab prophylaxis over no prophylaxis irrespective of prior history of immune tolerance induction (ITI) [25]. More than half of patients receiving emicizumab prophylaxis experienced zero bleeding events (Table 1) [19]. Intra-individual comparisons demonstrated that among patients who had participated in the non-interventional study, the annualized bleeding rate was significantly ($p < 0.0001$) reduced with emicizumab prophylaxis compared with previous episodic (group A; $n = 24$) or prophylactic (group C; $n = 24$) treatment with bypassing agents [26].

Emicizumab prophylaxis improved health-related quality of life (HR-QoL) [27]. In adolescents previously treated with prophylactic bypassing agents ($n = 13$), there were numerical improvements from baseline in Haemophilia-specific Quality of Life assessment for children and adolescents Short Form (Haemo-QoL-SF) domain and total scores. Among adult patients previously treated with episodic bypassing agents, the differences in adjusted mean Haemophilia-specific Quality of Life in adults questionnaire (Haem-A-QoL) total and physical health domain scores at week 25 significantly ($p \leq 0.003$) favoured emicizumab prophylaxis versus no prophylaxis. At week 25, 50–52% of patients receiving emicizumab prophylaxis versus 7% of patients receiving no prophylaxis achieved improvements from baseline in Haem-A-QoL total scores that exceeded the responder threshold (− 7 points). For Haem-A-QoL physical health domain scores, 72% of emicizumab recipients who were previously treated with episodic bypassing agents and 38% of those who were previously treated with prophylactic bypassing agents achieved improvements from baseline that exceeded the responder threshold (− 10 points), compared with 29% of patients receiving no prophylaxis [27].

Emicizumab prophylaxis was also associated with significant ($p < 0.05$) improvements in overall health status, as measured by the European Quality of Life 5-Dimensions 5-Levels (EQ-5D-5L) visual analogue scale (EQ-VAS) and EQ-5D-5L index utility score (IUS) [27]. At week 25, 57% of emicizumab recipients who were previously treated with episodic bypassing agents and 33% of those who were previously treated with prophylactic bypassing agents achieved improvements from baseline in EQ-VAS

Table 1 Efficacy of subcutaneous emicizumab for the prophylaxis of bleeding events in adults and adolescents aged ≥ 12 years with haemophilia A with or without factor VIII inhibitors in the HAVEN trials

Treatment regimen	No. of pts	Annualized bleeding rate[a] (95% CI)					Zero treated bleeds (% pts)
		Treated bleeds[b]	All bleeds	Treated spontaneous bleeds	Treated joint bleeds	Treated target joint bleeds	
With inhibitors (HAVEN 1) [19]							
Previously treated with episodic bypassing agents							
EMI 1.5 mg/kg q1w[c] (group A)	35	2.9 (1.7–5.0)**	5.5 (3.6–8.6)***	1.3 (0.7–2.2)***	0.8 (0.3–2.2)*	0.1 (0.0–0.6)**	63
No prophylaxis[d] (group B)	18	23.3 (12.3–43.9)	28.3 (16.8–47.8)	16.8 (9.9–28.3)	6.7 (2.0–22.4)	3.0 (1.0–9.1)	6
Previously treated with prophylactic bypassing agents							
EMI 1.5 mg/kg q1w[c] (group C)	49	5.1 (2.3–11.2)	6.5 (3.4–12.4)	3.1 (1.2–8.0)	0.6 (0.2–1.5)	0.3 (0.1–1.0)	69
Without inhibitors (HAVEN 3) [20]							
Previously treated with episodic FVIII							
EMI 1.5 mg/kg q1w[c] (group A)	36	1.5 (0.9–2.5)[†]	2.5 (1.6–3.9)[†]	1.0 (0.5–1.9)[†]	1.1 (0.6–1.9)[†]	0.6 (0.3–1.4)[†]	56
EMI 3 mg/kg q2w[c] (group B)	35	1.3 (0.8–2.3)[†]	2.6 (1.6–4.3)[†]	0.3 (0.1–0.8)[†]	0.9 (0.4–1.7)[†]	0.7 (0.3–1.6)[†]	60
No prophylaxis[d] (group C)	18	38.2 (22.9–63.8)	47.6 (28.5–79.6)	15.6 (7.6–31.9)	26.5 (14.7–47.8)	13.0 (5.2–32.3)	0
Previously treated with prophylactic FVIII							
EMI 1.5 mg/kg q1w[c] (group D)	63	1.6 (1.1–2.4)	3.3 (2.2–4.8)	0.5 (0.2–0.9)	1.2 (0.7–2.0)	0.6 (0.3–1.5)	56
HAVEN 4 [21]							
EMI 6 mg/kg q4w[c] (expansion cohort)	41	2.4 (1.4–4.3)	4.5 (3.1–6.6)	0.6 (0.3–1.5)	1.7 (0.8–3.7)	1.0 (0.3–3.3)	56

Endpoints assessed over a period of ≥ 24 weeks

EMI emicizumab, *FVIII* factor VIII, *pts* patients, *qxw* every *x* weeks

*$p < 0.01$, **$p < 0.001$, ***$p < 0.0001$ vs HAVEN 1 group B, [†]$p < 0.001$ vs HAVEN 3 group C

[a]Calculated using a negative binomial regression model

[b]Primary endpoint (group A vs group B in HAVEN 1; group A vs group C and group B vs group C in HAVEN 3)

[c]Maintenance dose (administered after four loading doses of 3 mg/kg once weekly). After ≥ 24 weeks, pts with suboptimal response (≥ 2 qualifying bleeds in the previous 24 weeks) could increase their maintenance dose to 3 mg/kg q1w

[d]Pts could switch to EMI prophylaxis after ≥ 24 weeks

scores that exceeded the responder threshold (+ 7 points), compared with 19% of patients receiving no prophylaxis. For EQ-5D-5L IUS scores, 48–50% of patients receiving emicizumab prophylaxis versus 13% of patients receiving no prophylaxis achieved improvements from baseline that exceeded the responder threshold (+ 0.07 points). The mean proportion of missed work days was lower with emicizumab prophylaxis than with no prophylaxis. Among patients who had previously received prophylactic treatment with bypassing agents, the mean proportion of missed work days during the previous 4 weeks was 9% at baseline and 3% during emicizumab prophylaxis. The proportion of missed school days was 28% baseline and 5% during emicizumab prophylaxis [27].

4.1.1.2 STASEY Preliminary results from the STASEY trial, which was primarily designed to evaluate emicizumab safety and tolerability, confirmed the efficacy of emicizumab prophylaxis in adults and adolescents aged ≥ 12 years with haemophilia A with inhibitors [22]. At data cut-off (October 2018), 88 patients (median age 28 years) had completed 24 weeks of treatment with subcutaneous emicizumab (3 mg/kg once weekly for 4 weeks, then 1.5 mg/kg once weekly thereafter) or had discontinued treatment, whichever occurred first. Annualized bleeding rates were low, and most (81%) patients experienced zero treated bleeds. Clinically meaningful improvements from baseline in HR-QoL and health status were observed across multiple domains, and most (95%) patients who completed the Emicizumab

Preference Survey (EmiPref) preferred emicizumab over their previous treatment [22].

4.1.2 In Patients Without Inhibitors (HAVEN 3)

HAVEN 3 enrolled 152 patients (median age 38 years) with haemophilia A without inhibitors [20]. Patients who had previously received episodic treatment with FVIII were randomized to receive subcutaneous emicizumab 3 mg/kg for 4 weeks followed by 1.5 mg/kg once weekly (group A) or 3 mg/kg every 2 weeks (group B) or to receive no prophylaxis (group C). Patients who had previously received prophylactic treatment with FVIII received subcutaneous emicizumab 3 mg/kg once weekly for 4 weeks, then 1.5 mg/kg once weekly thereafter (group D) [20].

Emicizumab prophylaxis significantly reduced the rate of bleeding events compared with no prophylaxis in adults and adolescents aged ≥ 12 years with haemophilia A without FVIII inhibitors [20]. For treated bleeds, the annualized bleeding rate over a period of ≥ 24 weeks was significantly reduced with emicizumab prophylaxis compared with no prophylaxis (primary endpoint; Table 1). Results were generally consistent across all subgroups regardless of age, race, bleeding rate in the 24 weeks prior to study entry and presence of target joints. Compared with no prophylaxis, emicizumab prophylaxis significantly reduced the annualized rates of all bleeds, treated spontaneous bleeds, treated joint bleeds and treated target joint bleeds (Table 1). More than half of patients receiving emicizumab prophylaxis experienced zero bleeding events (Table 1). According to intra-individual comparisons, the annualized bleeding rate was significantly ($p < 0.001$) reduced with emicizumab prophylaxis compared with previous FVIII prophylaxis in the non-interventional study (group D; $n = 48$) [20].

Patients receiving prophylaxis with emicizumab 1.5 mg/kg once weekly and 3 mg/kg every 2 weeks had improvements in the Haem-A-QoL physical health domain at week 25 of 12.5 points and 16.0 points, respectively, compared with patients receiving no prophylaxis [20]. At week 25, 44% of patients receiving emicizumab prophylaxis had a clinically meaningful ≥ 10-point change from baseline in Haem-A-QoL physical health score [28]. This improvement was maintained over the longer term, with scores improving by ≥ 10 points in 51% of patients at week 49 and 53% of patients at week 73 [28].

Most (94%) patients receiving emicizumab prophylaxis who completed the EmiPref survey preferred emicizumab over their previous treatment [29]. The most common reasons for preference included reduced frequency of administration, easier route of administration and fewer bleeding concerns. Most (90%) patients in group D who completed the Satisfaction Questionnaire–Intravenous Subcutaneous Hemophilia Injection (SQ-ISHI) were 'much more' or 'a lot more' satisfied with emicizumab than with FVIII prophylaxis [29].

4.1.3 Every-4-Week Dosage Regimen (HAVEN 4)

The findings of HAVEN 1 and 3 were supported by the results of HAVEN 4, which evaluated the efficacy of an alternative every-4-week dosage regimen of emicizumab [21]. This two-stage, non-randomized trial enrolled patients in a pharmacokinetic run-in cohort ($n = 7$) followed by a subsequent expansion cohort ($n = 41$). Results from the pharmacokinetic cohort are presented in Sect. 3. Patients in the expansion cohort (median age 39 years) had haemophilia A with ($n = 5$) or without ($n = 36$) inhibitors. All patients in the expansion cohort received subcutaneous emicizumab 3 mg/kg once weekly for 4 weeks, then 6 mg/kg every 4 weeks thereafter [21].

Emicizumab prophylaxis administered once every 4 weeks provided clinically meaningful bleeding control in adults and adolescents aged ≥ 12 years with haemophilia A [21]. In the expansion cohort, emicizumab prophylaxis maintained adequate control of bleeding, based on the annualized bleeding rates for treated bleeds, all bleeds, treated spontaneous bleeds, treated joint bleeds and treated target joint bleeds (Table 1). Annualized bleed rates were generally consistent across all prespecified subgroups regardless of bleeding rate in the 24 weeks prior to study entry, presence of target joints, previous type of treatment and FVIII inhibitor status. More than half of patients reported zero bleeds [21].

Emicizumab prophylaxis on an every-4-week dosage regimen was also associated with improvements in HR-QoL [21]. At week 25, the mean change from baseline in the Haem-A-QoL physical health score was − 15.41, which exceeded the responder threshold (≥ 10 points change). Indeed, 68% of patients reported a clinically meaningful change of ≥ 10 points in the Haem-A-QoL physical health score between baseline and week 25 [21], with similar results seen at week 49 (66%) and week 61 (71%) [28]. The mean proportions of missed school and work days in the previous 4 weeks were 5% and 12% at baseline and 1% and 3% at week 25, respectively [21]. Results of the EmiPref survey showed that all patients in the expansion cohort of HAVEN 4 preferred emicizumab over their previous treatment [29]. The most common reasons for preference included reduced frequency of administration, easier route of administration and generally better HR-QoL [29].

4.2 In Children Aged < 12 Years

4.2.1 In Patients with Inhibitors (HAVEN 2)

Subcutaneous emicizumab prophylaxis prevented or substantially reduced bleeding in children aged < 12 years with haemophilia A with inhibitors ($n = 85$) [23]. All patients had been previously treated with episodic or prophylactic bypassing agents. They received emicizumab 3 mg/kg once weekly for 4 weeks, followed by 1.5 mg/kg once weekly, 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks. Emicizumab prophylaxis was associated with clinically meaningful reductions in the rates of bleeding events, with most patients experiencing zero bleeding events (Table 2). An intra-individual comparison demonstrated that among patients aged < 12 years in the 1.5 mg/kg once weekly cohort who had participated in the non-interventional study ($n = 18$), the annualized rate of treated bleeds was reduced by 99% with emicizumab prophylaxis compared with previous bypassing agent treatment [23].

Emicizumab prophylaxis was associated with numerical improvements from baseline in total and physical health scores on the Haemo-QoL-SF and Adapted InhibQoL with Aspects of Caregiver Burden, an inhibitor-specific HR-QoL questionnaire [30]. The proportion of patients with no missed day care/school days in the previous 4 weeks was 28% at baseline and 83% at week 25 [30].

4.2.2 In Patients without Inhibitors (HOHOEMI)

The efficacy of subcutaneous emicizumab prophylaxis was also demonstrated in Japanese children aged < 12 years with haemophilia A without inhibitors ($n = 13$) [24]. All except one patient had been previously treated with FVIII prophylaxis. All patients received emicizumab 3 mg/kg once weekly for 4 weeks, followed by 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks. In an interim analysis (performed after ≥ 6 patients in both dosing cohorts had completed ≥ 12 weeks of treatment), emicizumab prophylaxis was associated with a clinically meaningful reduction in the rate of bleeding events (Table 2). Fifty percent of patients in the 3 mg/kg every 2 weeks group and 71% of those in the 6 mg/kg every 4 weeks group experienced zero bleeding events [24].

4.3 Surgical Experience

According to a pooled analysis of HAVEN 1–4, minor surgical procedures can be performed safely in patients with haemophilia A receiving emicizumab prophylaxis [31]. Across the four trials, a total of 113 patients underwent 214 minor surgical procedures (mostly dental and central venous access device procedures) and 19 patients underwent 19 major surgeries. Most (66%) minor surgeries were managed without prophylactic coagulation factor (FVIII or bypassing agents); 91% of these resulted in no treated postoperative bleeding. Most (84%) major surgeries were managed with prophylactic coagulation factor and only one of these resulted in a treated postoperative bleed. No

Table 2 Efficacy of subcutaneous emicizumab for the prophylaxis of bleeding events in children aged < 12 years with haemophilia A with or without factor VIII inhibitors

Treatment regimen[a]	No. of pts	Annualized bleeding rate[b] (95% CI)					Zero treated bleeds (% pts)
		Treated bleeds[c]	All bleeds	Treated spontaneous bleeds	Treated joint bleeds	Treated target joint bleeds	
With inhibitors (HAVEN 2) [23]							
EMI 1.5 mg/kg q1w	65	0.3 (0.17–0.50)	3.2 (1.94–5.22)	0.0 (0.01–0.10)	0.2 (0.08–0.29)	NE	77
EMI 3 mg/kg q2w	10	0.2 (0.03–1.72)	1.5 (0.62–3.40)	NE	0.2 (0.03–1.72)	0.2 (0.03–1.72)	90
EMI 6 mg/kg q4w	10	2.2 (0.69–6.81)	3.8 (1.42–10.11)	0.8 (0.05–12.00)	1.7 (0.60–4.89)	0.5 (0.05–5.88)	60
Without inhibitors (HOHOEMI) [24]							
EMI 3 mg/kg q2w	6	1.6 (0.60–4.25)					50
EMI 6 mg/kg q4w	7	1.0 (0.25–4.06)					71

EMI emicizumab, *NE* not estimable, *pts* patients, *qxw* every *x* weeks

[a]Maintenance dose (administered after 4 loading doses of 3 mg/kg once weekly)

[b]Calculated using a negative binomial regression model

[c]Primary endpoint

procedures resulted in death, thrombosis, FVIII inhibition or unexpected bleeding [31].

5 Tolerability of Emicizumab

Subcutaneous emicizumab was generally well tolerated when administered for the prophylaxis of bleeding episodes in patients with haemophilia A participating in the clinical trials discussed in Sect. 4. Discussion focuses on pooled data from HAVEN 1–4 and a dose-finding trial, in which 391 male patients with haemophilia A received at least one dose of emicizumab as routine prophylaxis [4]. Of these patients, 281 (72%) were adults, 50 (13%) were adolescents aged 12 to < 18 years, 55 (14%) were children aged 2 to < 12 years and five (1%) were infants aged 1 month to < 2 years. Across all trials, the median duration of exposure to emicizumab was 34.1 weeks (range 0.1–224.4 weeks) [4].

Adverse reactions occurring in ≥ 5% of emicizumab recipients were injection site reactions (ISRs; 22% of patients), headache (15%), arthralgia (15%), pyrexia (6%) and diarrhoea (6%) [4]. All ISRs were of mild to moderate intensity and most (93%) resolved without treatment. Four patients (1%) discontinued emicizumab because of adverse reactions [thrombotic microangiopathy (TMA), skin necrosis and superficial thrombophlebitis, headache and ISR] [4].

In an interim safety analysis of the STASEY trial (median duration of exposure 39 weeks), no new safety signals for emicizumab were identified and no thrombotic events were reported [22].

Emicizumab prophylaxis continued to be well tolerated over the longer term, according to a pooled analysis of HAVEN 1–4 ($n = 400$) [32]. The median duration of exposure to emicizumab in this analysis was 82 weeks; 77% of patients were treated for ≥ 74 weeks. The tolerability of emicizumab was similar to that reported previously, with no new safety signals identified [32].

5.1 Adverse Events of Special Interest

There is a (boxed [4]) warning regarding the risk of TMA and thromboembolism in patients receiving emicizumab and aPCC concomitantly [4–6]. In clinical trials, cases of TMA and thrombotic events were reported when, on average, a cumulative amount of > 100 U/kg/day of aPCC was administered for ≥ 24 h to patients receiving emicizumab prophylaxis [4, 6]. TMA was reported in three (0.8%) patients receiving emicizumab and at least one dose of aPCC [4]. Thrombotic events occurred in two (0.5%) patients receiving emicizumab and at least one dose of aPCC; neither of these events required anticoagulant therapy [4]. Evidence of improvement or resolution of TMA was observed within 1 week of discontinuation of aPCC, while thrombotic events improved or resolved within 1 month of discontinuation [4, 6]. One patient resumed emicizumab prophylaxis after resolution of TMA and one patient after resolution of a thrombotic event [4, 6]. One patient who developed TMA had a fatal outcome, although the investigator determined that TMA was resolving at the time of death [19]. If aPCC is coadministered with emicizumab, patients should be monitored for the development of TMA and thrombotic events [4–6]. If clinical symptoms and/or laboratory findings of TMA or thromboembolism occur, emicizumab should be interrupted and aPCC discontinued [4–6]. There were no safety concerns when emicizumab was used in combination with FVIIa or FVIII products [19–21, 33].

As with all therapeutic proteins, emicizumab has the potential for immunogenicity [4, 6]. Among emicizumab-treated patients in the HAVEN 1–4 trials, anti-drug antibodies (ADAs) were detected in 14 of 398 patients (3.5%), including three (< 1%) patients with ADAs with neutralizing potential [34]. One patient in HAVEN 2 developed neutralizing ADAs associated with loss of emicizumab efficacy after 5 weeks of treatment [4].

6 Dosage and Administration of Emicizumab

Subcutaneous emicizumab is approved in several countries worldwide. In the EU, it is approved for routine prophylaxis of bleeding episodes in patients (of any age) with haemophilia A (congenital FVIII deficiency) with inhibitors or severe haemophilia A (congenital FVIII deficiency, FVIII < 1%) without inhibitors [6]. In the USA, emicizumab is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and paediatric patients (newborn and older) with haemophilia A (congenital FVIII deficiency) with or without inhibitors [4]. In Japan, emicizumab is indicated for routine prophylaxis to control bleeding tendency in patients with haemophilia A (congenital FVIII deficiency) with or without inhibitors [5].

The recommended loading dose of emicizumab is 3 mg/kg once weekly for the first 4 weeks, followed by a maintenance dose of 1.5 mg/kg once every week, 3 mg/kg once every 2 weeks or 6 mg/kg once every 4 weeks [4–6]. The selection of a maintenance dose should be based on healthcare provider preference and patient adherence [4, 6]. Each subcutaneous injection should be administered at a different site (upper arm, abdomen or thigh) than the previous injection. Emicizumab may be self-administered (into the abdomen or thigh only) by the patient or caregiver following proper training in subcutaneous injection technique.

Self-administration is not recommended for patients aged < 7 years. Prophylaxis with bypassing agents should be discontinued the day before starting emicizumab [4, 6].

The results of clot-based assays (e.g. activated clotting time, aPTT and all aPTT-based assays) are affected by emicizumab [4, 6]. As such, these test results should not be used to monitor emicizumab activity, determine dosing for factor replacement or anticoagulation, or measure inhibitor titres [4, 6]. Local prescribing information should be consulted for full details regarding the administration of emicizumab, including further information on warnings and precautions, contraindications, interactions and use in special populations.

7 Place of Emicizumab in the Management of Haemophilia A

The primary goal in the management of haemophilia A is the prevention of joint damage and bleeding [35], preferably through replacement of the deficient clotting factor (i.e. FVIII) [1]. However, the use of conventional FVIII replacement products is limited by the need for frequent administration (owing to their short half-life) and the potential for inhibitor development (Sect. 1). Although bypassing agents can be used to treat bleeding episodes in patients with inhibitors, they are not ideal for long-term prophylaxis due to their low efficacy, high cost, inconvenience and increased risk of morbidity [2, 35]. The preferred strategy for inhibitor eradication is ITI therapy [3]. While most patients with inhibitors achieve successful immune tolerance to FVIII following ITI, approximately 20–40% of patients are intolerant of and/or unresponsive to ITI therapy [2, 3].

Emicizumab, a bispecific FIXa- and FX-directed antibody designed to mimic the cofactor activity of activated FVIII (Sect. 2), is the first non-factor replacement product to be approved for the prevention of bleeding episodes in patients with haemophilia A. Experts in the USA [36] and the UK [37] have issued evidence-based recommendations and consensus guidance for the use of emicizumab in patients with haemophilia A. Emicizumab was initially approved for the routine prophylaxis of bleeding episodes in adult and paediatric patients with haemophilia A with inhibitors [38]. This approval was based on the results of the HAVEN 1 trial, in which emicizumab prophylaxis significantly reduced the rate of bleeding events compared with no prophylaxis in adolescents and adults with haemophilia A with inhibitors (Sect. 4.1.1.1), and the HAVEN 2 trial, in which emicizumab prophylaxis prevented or substantially reduced bleeding in children with haemophilia A with inhibitors (Sect. 4.2.1).

The efficacy of emicizumab prophylaxis in haemophilia A was confirmed in HAVEN 3, which enrolled patients without inhibitors (Sect. 4.1.2), and HAVEN 4, which evaluated the efficacy of an alternative every-4-week dosage regimen (Sect. 4.1.3). Of note, HAVEN 3 also investigated alternative emicizumab dosage regimens in addition to the once weekly regimen, including once every 2 weeks and once every 4 weeks (Sect. 4.1.2). The results of HAVEN 3 and 4 led to extensions of the existing labels for emicizumab, to include patients with haemophilia A without inhibitors, and to provide two new dosage regimens (3 mg/kg every 2 weeks and 6 mg/kg every 4 weeks) in addition to the previously approved regimen of 1.5 mg/kg once weekly (Sect. 6) [4–6].

Psychosocial factors associated with haemophilia A can have a substantial impact on HR-QoL [39]. Therefore, it is important to minimize the impact of the disease on patients in terms of mental health, pain and disability, school and work attendance, and physical functioning [39, 40]. In clinical trials, emicizumab prophylaxis was associated with beneficial effects on HR-QoL and health status, including fewer missed work and school days (Sect. 4).

Emicizumab was generally well tolerated in clinical trials; the most common adverse reactions were ISRs, headache and arthralgia (Sect. 5). The management of bleeding episodes in patients with inhibitors receiving emicizumab prophylaxis is an important safety issue. Patients who experience breakthrough bleeding may require additional haemostatic treatment with bypassing agents (e.g. rFVIIa, aPCC) or FVIII [36]. Of note, rFVIIa is recommended for the first-line treatment of bleeding episodes, and aPCC should not be used unless no other option is available [37]. Emicizumab carries a special warning regarding the risk of TMA and thromboembolism in patients receiving concurrent aPCC (Sect. 5.1). To mitigate this risk, all patients receiving emicizumab in combination with aPCC should undergo regular monitoring. In clinical trials, cases of TMA and thromboembolism were reported in patients on emicizumab prophylaxis receiving > 100 U/kg/day of aPCC for ≥ 24 h, with evidence of improvement or resolution after aPCC discontinuation. The coadministration of FVIIa or FVIII products in patients receiving emicizumab prophylaxis appeared to be safe (Sect. 5.1).

Emicizumab interferes with all clot-based assays (Sect. 6), resulting in unreliable measurement of FVIII activity and inhibitor titres [41]. Due to the long half-life of emicizumab (Sect. 3), this interference may last up for to 6 months after the last administered dose [4]. Therefore, the measurement of FVIII activity and inhibitor titres during emicizumab prophylaxis (for example, in cases of breakthrough bleeding or major surgery) may pose a challenge [41, 42]. Alternative methods for measuring FVIII activity and inhibitor titres during emicizumab prophylaxis have been developed [41–44]. One-stage clotting assays are not useful, but FVIII activity and inhibitor titres can be measured using bovine chromogenic assays, while emicizumab

activity can be measured using human chromogenic assays [44]. In addition, the inclusion of anti-emicizumab monoclonal antibodies in routine one-stage coagulation assays has been shown to prevent emicizumab interference [41].

Emicizumab offers several advantages over conventional haemophilia A treatments; these may increase the uptake of and adherence to prophylaxis, thereby improving HR-QoL. Due to its extended half-life (Sect. 3), subcutaneous emicizumab can be administered potentially as infrequently as once every 4 weeks (Sect. 6), while other agents require more frequent intravenous administration (usually several infusions per week). The subcutaneous route of administration also provides a more convenient option for self-administration, which can be performed by the patient or caregiver following proper training (Sect. 6). Most patients in HAVEN 3 and all patients in HAVEN 4 expressed a preference for emicizumab prophylaxis over their previous treatment, citing reduced frequency of administration and easier route of administration as the most common reasons for their preference (Sect. 4.1). Extending the range of approved emicizumab dosing regimens may improve patient care by allowing clinicians to utilize a more individualized treatment approach [21].

Another phase III trial (HAVEN 5) is currently underway to investigate the efficacy, safety and pharmacokinetics of emicizumab prophylaxis (maintenance dosage of 1.5 mg/kg once weekly or 6 mg/kg every 4 weeks) versus no prophylaxis in 66 adult and adolescent patients aged ≥ 12 years with haemophilia A, regardless of inhibitor status (NCT03315455) [45]. Further studies are needed to determine the effects of emicizumab prophylaxis on long-term outcomes including joint/bone health, inhibitor development and risk of thrombosis [46]. A global, prospective, observational trial (MOTIVATE) has been designed to investigate the long-term (5-year) efficacy and safety of ITI and/or emicizumab in ≈ 120 patients with haemophilia A with inhibitors in a real-world clinical setting [47]. Study objectives include bleeding outcomes, joint health and adverse drug reactions (particularly thrombotic events) [47]. Results from this trial are awaited with interest.

Given the lifelong nature of haemophilia A, the costs of prophylactic FVIII replacement therapy are substantial [48]. In an independent cost-effectiveness analysis in patients with haemophilia A with inhibitors, emicizumab prophylaxis was projected to be cost-saving compared with bypassing agent prophylaxis or no prophylaxis [49]. Emicizumab prophylaxis provided gains in quality-adjusted life years at considerably lower costs compared with bypassing agents or no prophylaxis over a lifetime horizon [49]. Furthermore, modelled pharmacoeconomic studies in the USA (model inputs taken from the HAVEN trials) have also demonstrated cost savings with emicizumab relative to FVIII replacement therapy in patients with severe haemophilia A without inhibitors [50, 51]. Further robust pharmacoeconomic analyses, including long-term data, would be beneficial.

To conclude, in view of its convenient route of administration and versatile dosage regimens, subcutaneous emicizumab provides an effective and generally well-tolerated alternative to conventional FVIII replacement products for the prophylaxis of bleeding episodes in patients with haemophilia A, regardless of the presence or absence of inhibitors.

Data Selection Emicizumab: 352 records identified	
Duplicates removed	78
Excluded during initial screening (e.g. press releases; news reports; not relevant drug/indication; preclinical study; reviews; case reports; not randomized trial)	196
Excluded during writing (e.g. reviews; duplicate data; small patient number; nonrandomized/phase I/II trials)	27
Cited efficacy/tolerability articles	19
Cited articles not efficacy/tolerability	32
Search Strategy: EMBASE, MEDLINE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data. Key words were emicizumab, Hemlibra, haemophilia. Records were limited to those in English language. Searches last updated 2 September 2019	

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Compliance with Ethical Standards

Conflict of interest Hannah Blair is a salaried employee of Adis International Ltd/Springer Nature, is responsible for the article content and declares no relevant conflicts of interest.

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