INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Paper

Emicizumab: A Novel Bispecific Antibody Transforming Hemophilia A Treatment

Dr. D. Krishna Priyanka*, B. Priyanka, J. Sudheer Kumar, P. Anjali

Department of Pharmacy Practice,Hindu college of Pharmacy.

ARTICLE INFO

Published: 20 May 2026
Keywords:
Haemophilia A, Emicizumab, Factor VIII, Adverse Events, Hemostasis
DOI:
10.5281/zenodo.20308729

ABSTRACT

Haemophilia A is a hereditary bleeding disorder caused by deficiency of coagulation factor VIII, leading to prolonged bleeding episodes.Conventional treatment involves factor VIII replacement therapy, which is limited by the development of inhibitors in many patients.Emicizumab is a novel humanized bispecific monoclonal antibody developed as an alternative prophylactic therapy. It mimics the function of activated factor VIII by bridging activated factor IX and factor X. This mechanism restores thrombin generation and improves hemostasis. Unlike factor VIII, emicizumab has no structural homology, reducing immunogenicity risks. It is administered subcutaneously, offering greater convenience than intravenous therapies. The drug exhibits high bioavailability and a long half-life of 30–40 days. Flexible dosing schedules include weekly, biweekly, or monthly regimens. Clinical efficacy has been demonstrated in the HAVEN trial program. Significant reductions in annualized bleeding rates were observed across all studies. Many patients achieved zero treated bleeding events during long-term follow-up. Emicizumab is effective in patients with and without factor VIII inhibitors. It significantly improves patient quality of life and treatment adherence. The safety profile is generally favorable with mild adverse effects. Common side effects include injection site reactions, headache, and joint pain. Serious complications such as thrombotic events are rare but require monitoring. Drug interactions are minimal due to non-hepatic metabolism. Special considerations are required during surgical procedures and combination therapies.

INTRODUCTION

Haemophilia A is an inherited bleeding disorder caused by a congenital deficiency of factor VIII. It is characterized by a tendency for prolonged and excessive bleeding .The treatment of haemophilia A involves the use of factor VIII replacement therapy[1,7]

***Corresponding Author:** Dr.D.Krishna Priyanka
Address: *Department of Pharmacy Practice,Hindu college of Pharmacy..*
Email ✉: krishnapriyankadamarla@gmail.com
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The key structural features of the emicizumab molecule are as follows:

1**. Bispecificity** –Emicizumab possesses two different binding sites. One arm of the antibody binds activated factor IX (FIXa) , and the other binds factor X (FX) [2].

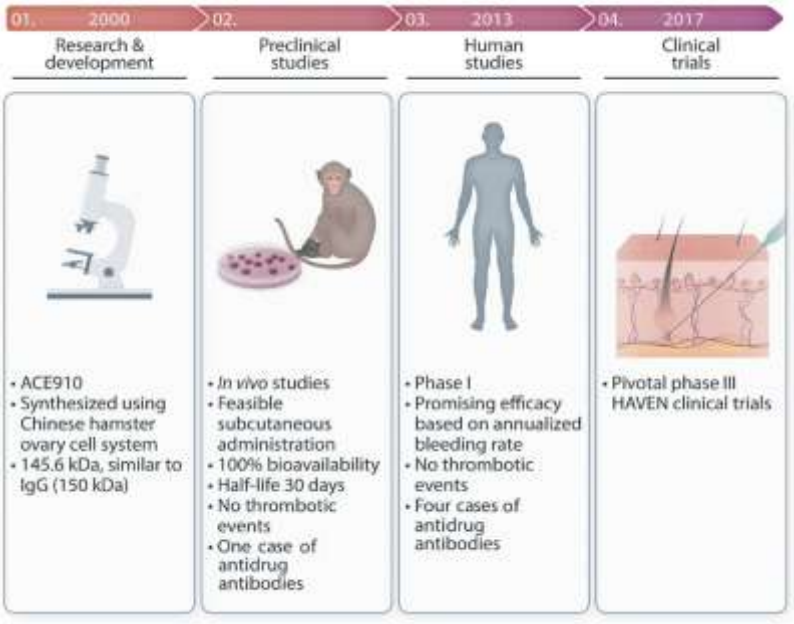
2. Humanization and IgG4 type –Structure was modified to resemble human antibodies as closely as possible (In this case immunoglobulin G4), which reduces the risk of an immune response . It is a monoclonal antibody, meaning all its molecules are identical [1,7]

3. Lack of homology with factor VIII – Emicizumab does not exhibit structural similarity or amino acid sequence homology with factor VIII (FVIII). It acts by mimicking the function of the missing or nonfunctional activated factor VIII (FVIIIa) in the coagulation cascade [1,7]

Development of emicizumab:

Over 2,400 engineered monoclonal IgG molecules were tested and methodically modified and optimized to minimize non-specific binding and immunogenicity and to maximize physicochemical stability and their activated factor VIII-cofactor activity, leading to the development of emicizumab. [22] In vivo studies were developed using primate models of acquired haemophilia A, in which bleeding events were successfully treated and prevented, and a once-weekly subcutaneous dosing provided the rationale for a prophylaxis protocol in people with haemophilia A. The first in-human study, started in 2013, was designed as a randomized and placebo-controlled, phase I trial using a single subcutaneous dose of emicizumab in healthy volunteers and demonstrated efficacy, high bioavailability from subcutaneous administration, without evidence of hypercoagulability[22].

These findings were corroborated in short-term and long-term extension studies (12 weeks to 33.3 months, respectively) of weekly subcutaneous administration to patients with severe haemophilia A over 12 years old with or without inhibitors, which showed a decrease in annualized bleeding rate close to zero, regardless of the presence of inhibitors, and four cases of antidrug antibodies, which were non-neutralizing and did not cause changes in treatment.



Fig;1-Development of Emicizumab:

HAVEN Clinical trails

[18(1–7) designed to evaluate the safety and efficacy of emicizumab (Hemlibra) for routine prophylaxis in haemophilia A patients with and without factor VIII (FVIII) inhibitors

Key HAVEN Studies

HAVEN 1:Evaluated emicizumab in adults and adolescents of Age 12 years with haemophilia A with inhibitors. It showed a 63% reduction in bleeds compared to no prophylaxis, and a 79% lower bleeding rate for those previously treated with bypassing agents (BPAs).[9,13]

HAVEN 2: Investigated once-weekly emicizumab in paediatric patients (<12 years) with inhibitors, finding that it was well-tolerated and reduced annualized bleed rates (ABR).[9,14]

HAVEN 3:Focused on patients of Age 12 years without inhibitors, demonstrating that emicizumab prophylaxis (once-weekly or every 2 weeks) was highly effective in reducing bleed rates.[9,15]

HAVEN 4: Evaluated adults and adolescents with/without inhibitors on a 4-weekly dosing schedule, confirming long-term efficacy and safety.[9,16]

HAVEN 6: Assessed efficacy and safety in individuals with mild or moderate haemophilia A without inhibitors, proving its value in patients with less severe forms of the disease.[17]

HAVEN 7: A study focusing on infants (newborn to 12 months) with severe haemophilia A, aimed at reducing early-life bleeding, including intracranial haemorrhage.[18]

Key Findings Across Studies (Long-Term Outcomes)

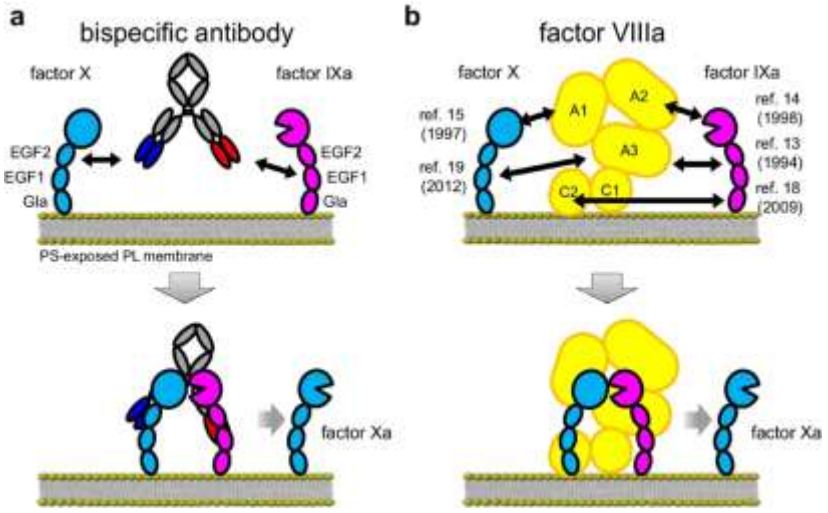
Efficacy: Across HAVEN 1–4, emicizumab maintained low bleed rates, with 82.4% of participants reporting zero treated bleeds during weeks 121–144.

Safety: The drug is well-tolerated with no new safety concerns in long-term follow-ups. The most common adverse events are injection-site reactions.

Warnings: Thrombotic microangiopathies (TMAs) and Thromboembolic events (TEs) were observed in HAVEN 1, specifically when high doses of aPCC (activated prothrombin complex concentrate) were used for breakthrough bleeds.

Mechanism of action

Due to its bispecific structure, emicizumab functions as a molecular "bridge" simultaneously binding FIXa (the enzyme) and FX (the substrate) on a phospholipid surface (e.g., activated platelets), thereby enabling Factor X activation by FIXa even in the absence of FVIIIa [1,2].



Fig;2-Mechanism of Action of Emicizumab

Production technology

Emicizumab is produced using recombinant DNA technology in Chinese hamster ovary (CHO) cells [1].

Molecular weight – The approximate molecular weight of emicizumab is 145.6 kDa [1].

Pharmacokinetics:

The pharmacokinetics of emicizumab include several key aspects that influence its effectiveness and use in the treatment of haemophilia.

Absorption:

Emicizumab shows high bioavailability when administered subcutaneously. The maximum plasma concentration (C_{max}) is reached within 1 to 3 days after administration [1,4].

The drug's absorption is dose-independent

Distribution:

Emicizumab exhibits wide distribution throughout the body, although it does not readily cross the blood–brain barrier. [1,4].

As a monoclonal antibody, it binds to plasma proteins and circulating cells, and its distribution is primarily limited to the intravascular and interstitial spaces. .

The drug distributes mainly within body fluids, including plasma, and in tissues where coagulation processes occur. [1,4].

Metabolism:

As a monoclonal antibody, it is metabolized mainly through the reticuloendothelial system (RES),which includes cells in the liver, spleen, and bone marrow.

Elimination:

Monoclonal antibodies such as emicizumab are broken down through proteolytic processes, in which proteolytic enzymes digest the molecule into smaller fragments that are subsequently eliminated from the body. [1,4].

This process is slower than the metabolism of synthetic drugs, contributing to the longer half-life of emicizumab.

Emicizumab does not rely on hepatic enzymes, This minimizes the risk of drug–drug interactions and makes emicizumab therapy safer and less susceptible to typical pharmacokinetic interactions seen with drugs metabolized in the liver. [1,4].

The half-life of emicizumab ranges from 30 to 40 days .[12]

Table:1-Pharmacokinetic parameters of Emicizumab

Parameters		Reference
Absorption	Efficient absorption and Dose Independent	[4,12]
C_{max}	Reached within 1 to 3 days after administration	[4,12]
Route of Administration	Subcutaneous	[4,12]
Bioavailability	High bioavailability when administered subcutaneously	[4,12]
Distribution	The drug distributes mainly within body fluids, including plasma, and in tissues where coagulation processes occur	[4,12]
Metabolism	Reticuloendothelial system (RES),which includes cells in the liver, spleen, and bone marrow	[4,12]
Elimination	Proteolytic enzymes digest the molecule into smaller fragments that are subsequently eliminated from the body	[4,12]
Half-life	30 to 40 days	[4,12]
Frequency	once weekly, or even every few weeks	[4,12]

Pharmacodynamic Effects

Mechanism of Action: Emicizumab mimics the cofactor function of FVIIIa. One arm binds to FIXa, and the other binds to FX, bringing them into close proximity to accelerate the activation of FX.

Thrombin Generation: Emicizumab restores thrombin generation, with mean peak heights reaching and maintaining levels that indicate effective coagulation, even in the presence of high-titer FVIII inhibitors.

aPTT Normalization: It significantly shortens and normalizes the activated partial thromboplastin time (aPTT), which is typically prolonged in haemophilia A patients.

FVIII-Like Activity: Emicizumab provides stable FVIII-equivalent activity, often correlating positively with serum concentration levels.

Effect on Coagulation Factors: The treatment does not require, nor does it affect, the activation steps of FVIII. It does not affect Prothrombin Time (PT).

Clinical Impact

Reduced Bleeding: It significantly reduces the Annualized Bleeding Rate (ABR) by 87–96% in clinical trials (HAVEN 1–4) in both patients with and without FVIII inhibitors.

Safety: It acts independently on FVIII inhibitors and does not produce inhibitors itself

Dosing Schedule:

Emicizumab is available as injection vials for single use in 4 different vial sizes: 30 mg/1.0 mL, 60 mg/0.4 mL, 105 mg/0.7 mL, and 150 mg/1.0 mL [. [5,6]].

The maintenance dosage regimens, according to the drug label, are 1.5 mg/kg weekly, 3 mg/kg every 2 weeks, or 6 mg/kg every 4 weeks (i.e, the dose per administration varies with body weight, but the dosing intervals are fixed). [5,6]

Given an individual's weight, the dose is unlikely to exactly match the content of the vial size suggested by the online Hemlibra calculator that is provided by the manufacturer, which often forces the prescribers to either overdose or discard the unused remainder of a vial. .[5,6]

Entire-vial–based dosing could be used to tackle these 2 issues. While maintaining the mg/kg dose according to the registered label, the prescriber could extrapolate the dosing interval to the nearest vial size. [5,6]

Who is appropriate to be considered for treatment with emicizumab?

Emicizumab is approved for PwHA (Patients with Haemophilia A) with or without inhibitor of any age.[8] Based on the clinical trial data, any PwHA with an inhibitor who has spontaneous or traumatic bleeding episodes, whether treated with episodic or prophylactic bypassing agent (BPA), will likely derive significant benefit from emicizumab prophylaxis and it should be considered first-line of therapy. Those on BPA prophylaxis with few bleeding episodes could consider switching from BPA prophylaxis to emicizumab prophylaxis based on overall cost-effectiveness, reduced administration burden and overall superior haemostatic efficacy.[8] In addition, infants should be considered for prophylaxis with emicizumab at any time after birth given the increased risk of intracranial haemorrhage prior to initiation of FVIII prophylaxis. At this time both FVIII prophylaxis and emicizumab prophylaxis should be considered therapeutic options for primary and secondary prophylaxis. Note, there are currently limited clinical trial data on the use of emicizumab in infants under 6 months of age and the pharmacokinetic exposure is likely to be less than in older infants and children.[8]

Recommendations for initiation of emicizumab

a. PwHA and Inhibitors

Administration of aPCCs should be discontinued at least 24 hours prior to initiation of emicizumab. [8]

b. PwHA and no inhibitors

FVIII prophylaxis continuation during the week after initiation of emicizumab is a common and reasonable approach. However, given that steady-

state levels of emicizumab are not achieved until after four weekly doses of 3 mg/kg, it may be reasonable to continue FVIII prophylaxis in select individuals based on their bleeding history and physical activity level, until they are ready to start maintenance dosing.

Standard patient education

i. Loading dose(s) should be given under medical supervision in order to review and observe self-administration technique. If the loading dose (in mg) is different than the maintenance, then patients should be educated about the dose and how to prepare it.[8]

ii. Emicizumab vials should be visually inspected for particulate matter and discoloration before administration. Emicizumab for subcutaneous administration is a colorless to slightly yellow solution.

iii. PwHA should know how to recognize bleeding events, follow the prescribed clotting factor product dose and frequency (FVIII concentrate or BPA for a breakthrough bleed, and reporting all bleeds to the HTC.[8]

iv. PwHA with inhibitors should understand that rFVIIa is the preferred BPA for management of acute bleeding due to risks of thrombosis and thrombotic microangiopathy (TMA) with activated Prothrombin Complex Concentrate (aPCC). Rarely low doses of aPCCs can be considered in management of acute bleeding events

Recommendations on surgical management with emicizumab

Emicizumab is approved for prophylaxis, but how this extends to surgical prophylaxis remains to be fully understood.

Emicizumab alone should not be presumed to be adequate for major procedures where current standards of care are to maintain factor levels within the normal range for a period of days.

Close monitoring of bleeding control as well as access to appropriate laboratory assays to monitor therapy (Eg: Chromogenic FVIII assay with FVIII replacement) is very important when determining treatment plans for patients on emicizumab needing surgical procedures.[8]

For major surgeries and procedures where bleeding could result in serious complications, patients should be provided rFVIIa or FVIII replacement pre- and post-operatively to maintain adequate haemostasis at the discretion of the treating physician. Anti-fibrinolytics may also be part of the perioperative management plan. Further research/experience is needed to form better defined treatment plans for different surgical procedures.

HAVEN Clinical trails

The HAVEN clinical trial program consists of several Phase 3 studies (1–7) designed to evaluate the safety and efficacy of emicizumab (Hemlibra) for routine prophylaxis in haemophilia A patients with and without factor VIII (FVIII) inhibitors

Key HAVEN Studies

HAVEN 1:Evaluated emicizumab in adults and adolescents of Age 12 years with haemophilia A with inhibitors. It showed a 63% reduction in bleeds compared to no prophylaxis, and a 79% lower bleeding rate for those previously treated with bypassing agents (BPAs).

HAVEN 2: Investigated once-weekly emicizumab in paediatric patients (<12 years) with inhibitors, finding that it was well-tolerated and reduced annualized bleed rates (ABR).

HAVEN 3:Focused on patients of Age 12 years without inhibitors, demonstrating that emicizumab prophylaxis (once-weekly or every 2 weeks) was highly effective in reducing bleed rates.

HAVEN 4: Evaluated adults and adolescents with/without inhibitors on a 4-weekly dosing

schedule, confirming long-term efficacy and safety.

HAVEN 6: Assessed efficacy and safety in individuals with mild or moderate haemophilia A without inhibitors, proving its value in patients with less severe forms of the disease.

HAVEN 7: A study focusing on infants (newborn to 12 months) with severe haemophilia A, aimed at reducing early-life bleeding, including intracranial haemorrhage.

Key Findings Across Studies (Long-Term Outcomes)

Efficacy: Across HAVEN 1–4, emicizumab maintained low bleed rates, with 82.4% of participants reporting zero treated bleeds during weeks 121–144.

Safety: The drug is well-tolerated with no new safety concerns in long-term follow-ups. The most common adverse events are injection-site reactions.

Warnings: Thrombotic microangiopathies (TMAs) and Thromboembolic events (TEs) were observed in HAVEN 1, specifically when high doses of aPCC (activated prothrombin complex concentrate) were used for breakthrough bleeds.

Side Effects:

Common Side Effects[3]

Injection site reaction (bruising, redness, pain, swelling) (22%)
Headache (15%)
Joint pain (15%)
Diarrhoea (6%)
Fever (6%)

Less Common Side Effects

Muscle pain from rhabdomyolysis (muscle breakdown)

Adverse Effects:

The most serious adverse effects occur when Activated Prothrombin Complex Concentrate (aPCC) is used to treat breakthrough bleeds while a patient is on emicizumab. [3]

Thrombotic Microangiopathy (TMA): Blood clots in small blood vessels, damaging the kidneys and other organs.

Thromboembolism: Serious blood clots, such as deep vein thrombosis (DVT) or pulmonary embolism.

Management: Avoid aPCC if possible; if required, limit the dose to less than 50 units/kg per 24 hours. [3]

Other Potential Effects

Anti-drug Antibodies (ADAs):

Some patients develop antibodies against emicizumab, which can occasionally make the drug less effective. [3] Emicizumab was associated with the development of antidrug antibodies in 5.1% of patients (34/668) who participated in the HAVEN 1-4 clinical trials.40 Most patients did not experience a change in emicizumab plasma concentrations or an increase in bleeding events; however, neutralizing antibodies were detected in <1% of cases and were presumed to be responsible for decreasing the plasma concentration of emicizumab and its subsequent loss of efficacy.

ADVANTAGES

Emicizumab offers several advantages over traditional therapies in Hemophilia A management:

1.It provides effective prophylaxis in patients both with and without factor VIII inhibitors.
2.The subcutaneous route of administration eliminates the need for frequent intravenous infusions.
3.Its long half-life enables less frequent dosing schedules, improving patient adherence.
4.It significantly reduces annualized bleeding rates and improves clinical outcomes.
5.The drug enhances quality of life by reducing

treatment burden and hospital visits.
6.It demonstrates a favorable safety profile with predominantly mild adverse effects.
7.Emicizumab has minimal drug–drug interactions due to non-hepatic metabolism.
8.It is suitable for use across all age groups, including pediatric patients.

Limitations:

The present review has few limitations
1.Long-term safety data of emicizumab are still evolving, especially in specific populations such as infants and elderly patients.
2.Limited evidence is available regarding its use in surgical settings and perioperative management.
3.Economic factors such as high cost and limited availability in developing countries were not explored in depth.
4. Comparative analysis with emerging therapies such as gene therapy was not extensively discussed.

DISCUSSION

Emicizumab has significantly advanced the management of Hemophilia A by providing an effective and convenient alternative to traditional factor VIII replacement therapy. Its unique bispecific mechanism restores coagulation function and demonstrates consistent efficacy across patients with and without inhibitors. Clinical trials have shown marked reductions in bleeding rates and improved patient outcomes. The subcutaneous route and extended dosing intervals enhance treatment adherence and quality of life. Despite these benefits, safety concerns such as thrombotic events, particularly with concomitant use of bypassing agents, require careful monitoring. Additionally, its high cost and limited data in certain clinical scenarios, such as surgical settings, remain challenges. Overall, emicizumab represents a promising and transformative approach, though further long-term and real-world studies are needed.

CONCLUSION

Emicizumab has emerged as a transformative therapy in the management of Haemophilia A, addressing key limitations of conventional factor VIII replacement. Its bispecific antibody mechanism effectively restores hemostasis by mimicking activated factor VIII function. Clinical evidence from multiple trials demonstrates a substantial reduction in bleeding rates across diverse patient populations. The subcutaneous route of administration and extended half-life significantly enhance patient compliance and quality of life. Importantly, its efficacy is maintained irrespective of the presence of factor VIII inhibitors. The safety profile is generally favorable, with predominantly mild and manageable adverseeffects. Nevertheless, careful monitoring is warranted when used concomitantly with bypassing agents due to thrombotic risks. Emicizumab also offers promising applications in paediatric and early prophylactic settings. Despite its high cost, its overall clinical benefits support its role as a cost-effective long-term strategy. In conclusion, emicizumab represents a paradigm shift and a cornerstone in modern haemophilia A prophylaxis.

Abbreviations:
PWHA: Persons with Haemophilia A
aPCC: Activated Prothrombin Complex Concentrate

REFERENCES

1. KoichiroYoneyama,ChristopheSchmitt.Agnès,Portron,etal.Clinical pharmacology of emicizumab for the treatment of hemophilia A 21 Aug 2023 ;Pages 775-790.

2. Franchini M, Mannucci PM. Hemophilia A in the third millennium. Blood Rev. 2013;27(4):179–184.
3. Shima M, Hanabusa H, Taki M, et al. Long-term safety and efficacy of emicizumab in a phase 1/2 study in patients with hemophilia A with or without inhibitors. Blood Adv. 2017;1(22):1891–1899.
4. Kiialainen A, Schmitt C, Adamkewicz JI, et al. Pharmacokinetics and biomarkers in persons with haemophilia A (PwHA) receiving emicizumab every 2 or 4 weeks. Haemophilia. 2019;25(Suppl 1):45–46.
5. Anouk,et al; The efficacy of the entire-vial dosing of emicizumab: Real-world evidence on plasma concentrations, bleeds, and drug waste**;** Volume 7, Issue 2100074 February 2023.
6. Clinical Review Report: Emicizumab (Hemlibra),Hoffmann-La Roche Ltd., Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2021 Feb.
7. Parth Mehta; Anil Kumar Reddy Reddivari.; Hemophilia; Update: June 5, 2023.
8. MASAC Document 268 - Recommendation on the Use and Management of Emicizumab-kxwh (Hemlibra®) for Hemophilia A with and without Inhibitors; 04/27/2022 ;Revisions: 255; 258.
9. Michael U Callaghan [1], Claude Negrier **;**Long-term outcomes with emicizumab prophylaxis for hemophilia A with or without FVIII inhibitors from the HAVEN 1-4 studies**;** Blood. 2021 Apr 22;137(16):2231-2242.
10. Shima M, Hanabusa H, Taki M, et al. Long-term safety and efficacy of emicizumab. Blood. 2017;130(22):2234–42.
11. Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. N Engl J Med. 2017;377:809–18.
12. Mahlangu J, Oldenburg J, Paz-Priel I, et al. Emicizumab pharmacokinetics. Blood. 2018;132(19):2036–44
13. Oldenburg J, et al. HAVEN 1 trial. N Engl J Med. 2017;377:809–18.
14. Young G, et al. HAVEN 2 trial. Blood. 2019;134(24):2127–38.
15. Mahlangu J, et al. HAVEN 3 trial. N Engl J Med. 2018;379:811–22.
16. Pipe SW, et al. HAVEN 4 trial. Lancet Haematol. 2019;6(6):e295–305.
17. Callaghan MU, et al. HAVEN 6 study. Haemophilia. 2022;28(3):393–401.
18. Shima M, et al. HAVEN 7 study. Blood. 2023;141(5):556–65.
19. Pasi KJ, et al. Long-term emicizumab outcomes. Blood. 2020;135(26):2233–42.
20. Peyvandi F, et al. New therapies in hemophilia. Lancet. 2016;388(10040):187–97.
21. Tiede A, et al. Safety of emicizumab. J Thromb Haemost. 2018;16(11):2216–27.
22. Pedro E. Alcedo Andrade , Pier Mannuccio Mannucci , Craig M. Kessler ; Emicizumab: the hemophilia A game-changer; Vol. 109 No. 5 (2024): May, 2024

HOW TO CITE: Dr. D. Krishna Priyanka, B. Priyanka, J. Sudheer Kumar, P. Anjali, Emicizumab: A Novel Bispecific Antibody Transforming Hemophilia A Treatment, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 5, 5187-5195, https://doi.org/10.5281/zenodo.20308729