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Cost-effectiveness of emicizumab prophylaxis for haemophilia A with inhibitors: an adaptive health technology assessment for the Indian setting

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Abstract

Objective To assess the cost-effectiveness of emicizumab prophylaxis for patients having haemophilia A with inhibitors in the Indian context using an adaptive health technology assessment (aHTA) methodology.

Design Economic evaluation using multiple approaches aimed at adjusting previously generated cost-effectiveness results based on (1) price differences only ('simple') and (2) differences in cost and expected treatment duration ('moderate') and differences in cost, inflation and life expectancy ('complex').

Setting Typical haemophilia care in India.

Participants Patients with haemophilia A and inhibitors.

Intervention Emicizumab prophylaxis using two vial strengths (30 or 150 mg/mL) in comparison to no prophylaxis.

Main outcome measures Adjusted incremental cost-effectiveness ratio (ICERa), incremental costs and incremental quality-adjusted life years associated with emicizumab prophylaxis from both the health system and societal perspectives.

Results Using the simple ICER adjustment method, emicizumab prophylaxis resulted in potential cost savings from the payers' perspective for both vial strengths in patients aged ≥12 and <12 years. However, from a societal perspective, emicizumab prophylaxis was not cost-effective. Using the moderate adjustment method, emicizumab prophylaxis showed potential cost saving from the health system perspective. The complex adjustment method also revealed cost savings for emicizumab prophylaxis from the health system and societal perspectives across different age groups.

Conclusion We found that implementing emicizumab prophylaxis for patients with haemophilia A and inhibitors in India has the potential to result in cost savings. This study highlights the feasibility of using the expanded aHTA methodology for rapid evidence generation in the Indian context. However, it is crucial to address certain research gaps, including data limitations, challenges in translating international evidence to Indian context and associated uncertainties. Additionally, conducting a comprehensive budget impact analysis is necessary. These findings hold significant implications for decision-making regarding the potential provision of emicizumab prophylaxis through federal or/and state government-funded programmes and institutions in India.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Limited understanding exists regarding the cost-effectiveness of emicizumab prophylaxis for patients with haemophilia A and inhibitors in India. Our study fills this gap by employing an expanded adaptive health technology assessment (aHTA) methodology.

WHAT THIS STUDY ADDS

⇒ We found that implementing emicizumab prophylaxis in India has the potential to result in cost savings. Additionally, we demonstrated the feasibility of using the expanded aHTA methodology for rapid evidence generation in the Indian context.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings have significant implications for practice and policy decisions regarding the provision of emicizumab prophylaxis through federal or/and state government-funded programmes and institutions in India. The study contributes to the research and body of evidence on the application of pragmatic or aHTA methods and highlights limitations encountered due to research gaps, data constraints and challenges in adapting international evidence to the country context.

Introduction

Haemophilia affects a significant number of individuals worldwide, particularly the developing countries. In India, the expected number of affected individuals is 1 lakh, with only about

15 218 patients registered.[1 2] Treatment for haemophilia involves lifelong therapy to replace the missing clotting factor, either as prophylactic treatment or as needed for bleeding episodes. The costs associated with clotting factor usage form a substantial portion of haemophilia drug expenses. Additionally, direct costs include expenses related to haemarthroses, infections, hospitalisations and surgical procedures to replace damaged joints while productivity losses contribute to significant indirect costs.[1 3]

A major complication for patients with haemophilia A is the development of inhibitors, which greatly impact their quality of life.[4] The global prevalence of inhibitors among patients with severe haemophilia A ranges from 20% to 40%[5 6] and in India, the estimated prevalence is 19.5%.[7] Bypassing agents (BPAs) are administered to manage bleeding episodes and are also employed as a prophylactic measure to safeguard against potential bleeding complications associated with invasive procedures.[4]

Currently, in India, the treatment approach for patients having haemophilia A with inhibitors primarily involves on-demand treatment using BPAs. The administration of BPA prophylaxis incurs significant costs as it requires frequent intravenous injections, typically three times a week. This regimen presents challenges for patients and their families, including the need for repeated painful injections, difficulty in accessing intravenous sites in small children and the inconvenience of travelling to distant hospitals for treatment.

In the recent years, the emergence of emicizumab, a novel monoclonal antibody that mimics factor VIII, has shown promising results in reducing bleed frequency and improving the quality of life for individuals with haemophilia A. Clinical trials, such as HAVEN 1, 2, 4 and 5, have demonstrated a significant reduction in bleeding episodes among patients with inhibitors receiving emicizumab prophylaxis compared with those without prophylaxis and those on BPA prophylaxis.[8–11]

Further, emicizumab, being a subcutaneous injection, offers a more convenient and patient-friendly treatment option. Emicizumab can be administered weekly, every 2 weeks or every 4 weeks, and parents can administer it at home. For patients with inhibitors, it is usually administered weekly. Studies have proved that emicizumab demonstrates better haemostatic efficacy and safety profiles in comparison to BPA prophylaxis.[12] Therefore, introducing emicizumab in India could address the existing limitations associated with treatment using BPAs, resulting in potential improvements in patients' quality of life, productivity and reduction in healthcare costs. Various economic evaluations conducted in other countries and health technology assessment (HTA) reports have also recognised emicizumab as cost-effective option for patients with inhibitors.[13–17] But, the evidence on this regard is currently lacking in India.

Given the limited accessibility of emicizumab prophylaxis in India, we aimed to assess its cost-effectiveness for patients with haemophilia A and inhibitors. Given the level of urgent interest in this treatment and limitations on capacity to conduct formal economic evaluation using local data, we used a novel adaptive HTA (aHTA) methodology. For evidence synthesis step of this aHTA work, we adopted key methodological aspects of rapid evidence synthesis (RES) approach aiming to rapidly synthesise the evidence required for undertaking the aHTA.

The study also aimed to provide insights into the feasibility of implementing this aHTA methodology in the Indian context. The findings of this exploratory research will inform decision-making regarding the use of emicizumab in the Indian healthcare system, particularly as governments like the state of Punjab and Union Territory of Jammu and Kashmir are considering its delivery at public hospitals. This study also offers valuable information for other states and centrally funded health systems in the country to consider emicizumab prophylaxis as a standard care option.

Methodology

Study approach

Traditional HTA is a process of evaluating health technologies to identify the most cost-effective interventions, maximising health outcomes per investment. It is a resource-intensive, data-driven process that employs systematic methodologies and explicit procedures to optimise the allocation of limited healthcare resources in support of informed policy decisions. While developed countries typically conduct traditional HTAs to inform healthcare system inclusion decisions, low and middle-income countries with nascent HTA systems face challenges in conducting traditional HTAs due to time constraints, shortage of expertise, data and sufficient resources.[18–20]

In circumstances where a full HTA is not practical, such as a stated urgent timeline to address an important health policy need or lack of trained personnel and general resources for traditional HTA, aHTA approaches have emerged as a means to expedite evidence-informed policy decisions. aHTA is a structured 'fit for purpose' approach to conducting the optimal HTA analysis. They produce efficient HTA results by adjusting for analytical time, data, capacity and source of conduct, leveraging information from other settings where possible. These approaches modify or use international data, traditional economic evaluations, models and conclusions from existing HTA agencies while considering its transferability to the local context and uncertainty related to any transfer.[21]

Globally, developed countries like the UK, Canada and the European Union, and developing countries including Romania, Argentina and India have already developed and employed aHTA methodologies.[21 22] In this study, we have expanded on these aHTA methodologies and developed a four-step aHTA process to assess the cost-effectiveness of emicizumab prophylaxis in India, considering the imbalance between volume of policy decisions and capacity for de novo modelling that currently exists in the country. This approach holds potential for informing decisions related to healthcare provisioning in India and also expediting policy decisions regarding cost-effective health technologies, as evaluated through traditional HTAs conducted elsewhere.

The genesis for developing this aHTA methodology, and the initial steps taken for deciding on the topic are detailed in the online supplemental file 1 under the subheading 'Topic selection'. Following this, we developed the PICO components for the study:

- Population—patients with haemophilia A with inhibitors.
- Intervention—emicizumab prophylaxis.
- Comparator—no prophylaxis (ie, on-demand treatment using BPAs).
- Outcomes—reduction in annualised bleeding rates (online supplemental table 1).

The four steps employed for conducting the study are described below.

Step 1: topic prioritisation

The first step in the aHTA process is ensuring that the topic is of sufficiently high priority in the local setting. To determine this, we considered various criteria, including expert consultations to assess the topics' relevance, the magnitude of the health problem, clinical and economic impact, feasibility, availability and relevance of evidence, urgency for a health policy need and social

value judgements. The specific aspects of these criteria that led to ascertaining the high priority of this topic are described in the online supplemental file.

Step 2: conducting RES

Following the topic prioritisation, we initiated the RES process to conduct an initial rapid assessment of available evidence for undertaking the aHTA on the topic. We adopted key methodological aspects of RES approach which is designed to conduct rapid assessment of existing evidence to inform a time-bound (short time span) healthcare decision-making.[23] 24 We initiated the RES process by providing a comprehensive description of the decision problem, namely the clinical benefits, risks and cost-effectiveness of emicizumab prophylaxis when compared with no prophylaxis in India. This involved contextualising the decision problem within the Indian healthcare setting and defining the relevant parameters, such as population, intervention, comparisons and outcomes, that would guide the assessment.

We revisited and expanded on the PICO framework by reassessing the parameters of the study to align with existing evidence on the 'emicizumab' and 'no' prophylaxis groups. Once the PICO framework and the information required for conducting this aHTA were determined, we initiated the rapid literature search to identify the evidence. The protocol developed for the RES approach is included in the online supplemental file 1.

Step 3: acquiring evidence

We adopted a pragmatic and iterative process for acquiring evidence. Initially, our search query was tailored to conduct a narrow search to maximise relevance, before broadening the search approach. We conducted rapid searches across three key data sources to gather evidence on the clinical impact and cost-effectiveness of emicizumab prophylaxis: (1) HTA agency reports, (2) published systematic reviews and cost-effectiveness analyses (CEA) and (3) newly published clinical evidence (figure 1). We also conducted reference checking to identify any additional evidence. The search query used in this stage is presented in the online supplemental file 1.

We also consulted clinical experts treating patients with haemophilia A to gather any additional evidence on the topic. We continued the step 3 until sufficient intervention-specific evidence was identified. Full text of the identified literature was reviewed for data extraction. To ensure consistency and facilitate comparisons across the selected documents, a data extraction template was used. This template served as a standardised tool for aggregating information and reporting the collected data uniformly. It included background information on the type of evidence and extracted critical findings related to the effectiveness, safety, cost-effectiveness and other pertinent aspects of the intervention (online supplemental tables 2–4).

Step 4: evidence appraisal and cost-effectiveness synthesis

On completion of data collection of available evidence on the topic in step 3, we proceeded to appraise the full evidence package. The aim was to provide a comprehensive assessment of the accumulated information, including the effectiveness, cost-effectiveness, safety, level of confidence in the evidence and any remaining uncertainties that should be taken into account. By employing the RES approach, we appraised a range of seminal work from reputable sources in a short time frame, at the same time we ended up collecting necessary information required for the 'cost effectiveness synthesis'. We concluded the RES process by producing a narrative summary to report the intervention and cost-effectiveness effect estimates along with their appraisal of certainty and relevance. Further details regarding information sources, search strategy, search queries, data extraction, data charting process, risk of bias assessment and the strategy to data synthesis are presented in the online supplemental file.

For the cost-effectiveness synthesis, since the collected information on costs, health benefits and incremental cost-effectiveness ratios (ICERs) originated from diverse settings, adjustments were made to increase their potential applicability to the Indian context. Three adjustment methods were employed, each of which is intended to reflect the fact that an aHTA approach will not have the luxury of access to an operating and modifiable economic model, only published model findings. For ease of interpretation, they are known as 'simple', 'moderate' and 'complex' adjustments based on the number of data steps and assumptions required. As noted below, each of the three adjustments requires assumptions and has limitations; for this reason, all approaches were implemented to evaluate the consistency of findings, taking the available data into consideration. Detailed description of the methods

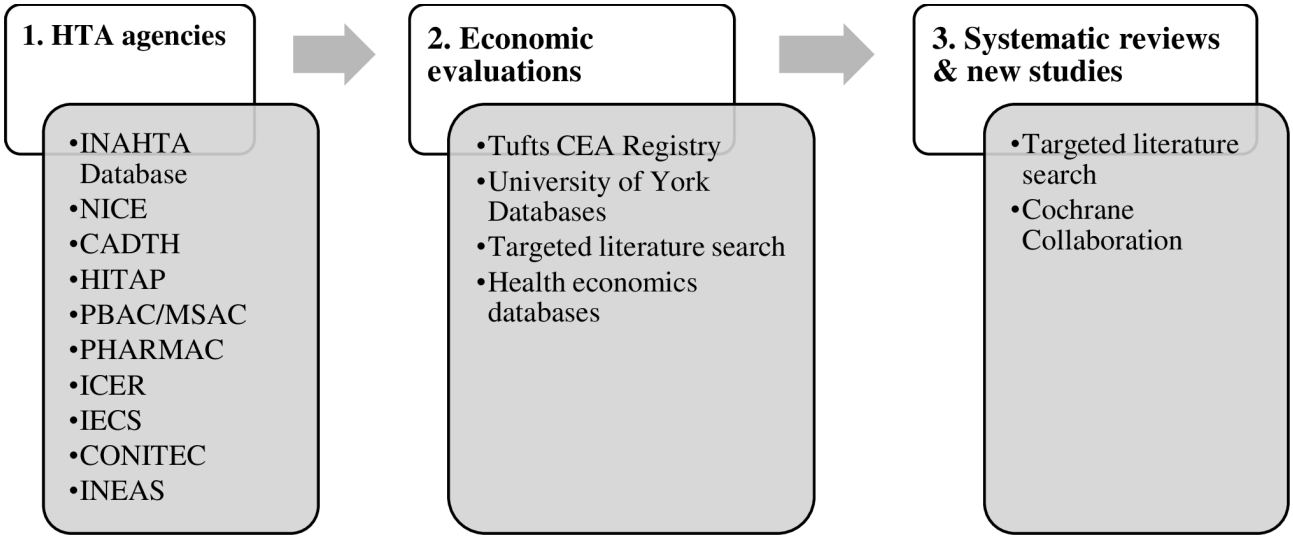

Figure 1 Hierarchical selection of potential sources of evidence. HTA, health technology assessment.

can be found in the online supplemental file 1, and the input parameters used for the adjustments are provided in table 1.

ICER adjustment methods

Simple adjustment

To perform a simple adjustment, the study-reported ICER was multiplied by the ratio of the price of emicizumab in India (P_A) to the price in the original study country (Po), as noted below:

$$ICER_A = ICER_O \times (P_A/P_O)$$

The simple adjustment requires accurate estimates of the intervention price in both settings, assumes that intervention price is the dominant driver of cost-effectiveness findings and may be of lower utility when the distribution of costs is more complex or when other parameters are significant drivers of findings.

Moderate adjustment

The moderate adjustment method estimated the monthly treatment cost (Ci) and the duration of therapy (in months) for both the intervention and its comparator (Mi and Mc, respectively) based on data from the original clinical study or CEA. The formula for the moderate adjustment was as follows:

$$ICERi = (Ci \times Mi) - (Cc \times Mc)/((MiMc)/12)$$

where Ci and Cc represent the monthly cost, and Mi and Mc represent the number of months of treatment for the intervention and comparator, respectively. The moderate adjustment requires detailed estimation of monthly cost for both intervention and comparator and assumes the availability of data to estimate typical duration of therapy. If this is not directly available from a clinical trial, expert opinion may be required, which may limit the applicability and generalisability of the estimates.

Complex adjustment

In situations where multiple expenses, beyond the intervention cost, or variations in disease characteristics between countries needed to be considered, a more sophisticated formula was employed. This involved separate adjustments for costs and quality-adjusted life years (QALYs). The detailed formula is included in the online supplemental file 1; in brief, costs are adjusted for both purchasing power parity (PPP) and inflation, and QALYs are adjusted for differences in life expectancy across settings. PPP and inflation indices are typically accessible via public sources, but the underlying assumption that these factors largely explain cost differences may be challenging, as differences in infrastructure and settings of care may also differ substantially between countries. In addition, life expectancy adjustment should ideally be made from the time of diagnosis of a given disease, but these data may only be available from birth.

We conducted a comprehensive evidence appraisal and employed all three adjustment methods to enhance the robustness of the CEA and assess comparability of adjusted ICERs (ICERa) in the Indian context after accounting for factors such as price differentials, duration of therapy, cost variations, inflation and epidemiological differences between countries. In the analysis, India's per capita gross domestic product ($2256.59; ₹185 605) was considered as the cost-effectiveness threshold.

After a careful appraisal of the evidence in step 4, the key parameters necessary for the ICER adjustment methods, including ICERs, costs and QALYs for both the intervention and comparator relevant to this study, were obtained from the cost-effectiveness report published by the Institute for Clinical and Economic Review.[16] Data required on the total number of bleeds per year among ≥12 and <12 years age group patients in the moderate adjustment method, certain patient-related parameters such as mean weight of different age group patients, mean treatment duration, drug costs, life expectancy and number of bleeding episodes were obtained from expert opinion. Various data used for the analysis are presented in table 1.

Results

In this study, a team of six researchers, comprising three junior and three senior-level researchers, conducted the project alongside their other responsibilities. The project lasted 4 months from March to June 2023. The junior researchers dedicated approximately 60 hours each from conceptualisation to manuscript writing, while the senior researchers contributed around 20 hours each. Additionally, two expert clinicians were involved for consultations who were specialised in the treatment of patients with haemophilia in India.

As per the RES methodology, a narrative summary of the evidence used for the aHTA is presented in the online supplemental file 1. The narrative summary included the information synthesis on intervention effects, and the cost-effectiveness along with their critical appraisal as reported in the report published by the Institute for Clinical and Economic Review, USA, from which the data required for this aHTA were obtained. Other HTA studies sourced from the literature search either did not align with the study's PICO or did not report the parameters relevant to this study.

Data collected at the end of RES process are presented in online supplemental tables 2–4. We did not conduct evidence appraisal of each study/report identified at the end of RES process as they were not used as input parameters in the aHTA and did not aim to present a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram that are mainly recommended for traditional systematic reviews.

We used the economic evaluation conducted by the Institute for Clinical and Economic Review, USA, to inform the ICERa in the Indian context. The Institute for Clinical and Economic Review's report conducted comparisons of the cost-effectiveness of emicizumab prophylaxis with no prophylaxis in patients aged ≥12 and <12 years, considering both the health system and societal perspectives. The report revealed that emicizumab resulted in greater QALYs while also being cost saving in terms of total costs, when compared with no prophylaxis, from both health system and societal perspectives.

Simple adjustment

We found that providing emicizumab prophylaxis using the vial strength of 30 mg/mL resulted in cost savings from the payers' perspective for both age groups (<12 and ≥12) of patients in India. Costs were lowered by −$8 913 222 (−₹733 112 509) with an incremental QALY of 0.91 for patients ≥12 years old, and −$10 329 148 (−₹849 572 423) with an incremental QALY of 2.39 for patients <12 years old. However, from the societal perspective, giving emicizumab prophylaxis using this vial strength was not cost-effective. Similar results were observed for the vial strength of 150 mg/mL, where cost savings were seen from the payers' perspective for both the age groups, but it was not cost-effective from the societal perspective for both age groups of patients in India (table 2).

Moderate adjustment

The total cost of treatment for patients on no prophylaxis was higher ($163 777 751; ₹13 470 720 019) when compared with the

Table 1 Input parameters used for the ICER adjustment methods

Parameters	₹	$	Reference
Simple adjustment (payer's perspective)			
ICERo (<12 years old)	−344 673 971	−4 190 565	ICER report
ICERo (≥12 years old)	−806 100 255	−9 800 611	ICER report
Simple adjustment parameters (societal perspective)			
ICERo (<12 years old)	360 754 763	4 386 076	ICER report
ICERo (≥12 years old)	838 631 936	10 196 133	ICER report
Cost parameters			
PA (drug price in India) for 30 mg/mL (as of 19 April 2023)	58 900		Manufacturer (Roche Medical Information)
Po (drug price in USA) for 30 mg/mL (as of 19 April 2023)	282 499	3435	www.drugs.com/price-guide/hemlibra
PA (drug price in India) for 150 mg/mL (as of 19 April 2023)	294 392		Manufacturer (Roche Medical Information)
Po (drug price in USA) for 150 mg/mL (as of 19 April 23)	1 409 369	17 135.18	www.drugs.com/price-guide/hemlibra
Cost parameters for moderate adjustment			
Cost of EMI per vial (30 mg/mL)	58 900		Manufacturer (Roche Medical Information)
Mean dose per kilogram body weight (mg/kg) per month	6		Expert opinion
Mean weight of patients on prophylaxis (kg), 2–5 years	12		Expert opinion
Mean weight of patients on prophylaxis (kg), 6–10 years	25		Expert opinion
Mean weight of patients on prophylaxis (kg), 6–10 years	44		Expert opinion
Mean duration of treatment (in months) (Mi)	420		Expert opinion
Cost of BPA per vial (500 IU)	80 000		Expert opinion
Mean duration of patients on FEIBA (Factor eight inhibitor bypass activity) regimen (in months) (Mc)	300		Expert opinion
Dose per kilogram body weight (IU)	500		Expert opinion
Frequency of administration (per day)	2		Expert opinion
Approximate number of bleeding episodes per month	2		Expert opinion
Complex adjustment			
PPP GDP for study country (USA)		59 915	World Bank data
PPP GDP for study country (India)		6112.0	World Bank data
Consumer Price Index (CPI) for health in India for current year (2023)		183.4	MOSPI, Government of India
CPI for health in India for publication year (2018)		135.2	MOSPI, Government of India
Life expectancy from birth in study country (USA)		78.54	World Bank data
Life expectancy from birth in India		70.47	World Bank data
Reduction in life expectancy (in years)		10	Expert opinion
Life expectancy from disease in study country (2017)		68.54	Calculated
Life expectancy from disease in India (2017)		60.47	Calculated
Health system perspective			
Emicizumab prophylaxis (≥12 years old)		19 221 932	ICER report
No prophylaxis (≥12 years old)		28 135 154	ICER report
Emicizumab prophylaxis (<12 years old)		20 683 787	ICER report
No prophylaxis (<12 years old)		31 012 935	ICER report
Societal perspective			
Emicizumab prophylaxis (≥12 years old)		19 623 275	ICER report
No prophylaxis (≥12 years old)		28 901 756	ICER report
Emicizumab prophylaxis (<12 years old)		21 212 892	ICER report
No prophylaxis (<12 years old)		31 695 614	ICER report
Study-reported QALYs (2017)			
Emicizumab prophylaxis (≥12 years old)	15.41		ICER report
No prophylaxis (≥12 years old)	14.5		ICER report
Emicizumab prophylaxis (<12 years old)	22.79		ICER report
No prophylaxis (<12 years old)	20.4		ICER report

BPA, bypassing agent; EMI, emicizumab; GDP, gross domestic product; ICER, incremental cost-effectiveness ratio; PPP, purchasing power parity; QALY, quality-adjusted life year.

Table 2 Adjusted incremental cost-effectiveness ratios (ICERa) for different vial strengths of emicizumab among patients with haemophilia A and inhibitors compared with those without prophylaxis using the simple adjustment method for payers and societal perspectives in India

		Emicizumab (30 mg/mL)		Emicizumab (150 mg/mL)	
Perspective	Age group	ICERa* (₹)	ICERa* ($)	ICERa* (₹)	ICERa* ($)
Payers	<12	Cost saving	Cost saving	Cost saving	Cost saving
Payers	≥12	Cost saving	Cost saving	Cost saving	Cost saving
Societal	<12	75 216 001	914 480	75 355 248	916 173
Societal	≥12	174 851 580	2 125 855	175 175 281	2 129 791

*The exchange rate used was ₹82.25 for US$1, as of 15 May 2023.

total cost of treatment for patients on emicizumab prophylaxis ($2 525 965; ₹207 760 621). The mean duration of treatment among patients on emicizumab prophylaxis (Mi) is estimated to be 10 years longer when compared with patients on 'no prophylaxis' (Mc). The ICERa indicated that implementing emicizumab prophylaxis could be cost saving from the health system perspective in India (table 3).

Complex adjustment

From the health system perspective, implementing emicizumab prophylaxis resulted in cost savings. For patients aged <12 years, the costs were lowered by –$1 429 359 (–₹117 564 777), with an incremental adjusted QALY of 2.11. Similarly, for patients aged ≥12 years, the costs were lowered by –$1 233 421 (–₹101 448 877), with an incremental adjusted QALY of 0.8. These findings highlight the cost-saving potential of emicizumab prophylaxis from the health system perspective.

From the societal perspective, emicizumab prophylaxis also demonstrated cost savings. For patients aged <12 years, costs were lowered by –$1 450 611 (–₹119 312 754), with an incremental adjusted QALY of 2.11 compared with no prophylaxis. Likewise, for patients aged ≥12 years, costs were lowered by –$1 283 966 (–₹105 606 203), with an incremental adjusted QALY of 0.8. These results indicate that implementing emicizumab prophylaxis can be a cost-saving approach across different perspectives and age groups in India compared with the current no prophylaxis scenario (table 4).

Table 3 Adjusted ICERs for emicizumab prophylaxis among patients with haemophilia A and inhibitors compared with those without prophylaxis in India using the moderate adjustment method

Parameters	Values
Monthly cost ($) of emicizumab (EMI) intervention (Ci)	1918
Mean duration of treatment (in months) for different patient age groups (Mi)	
2–5 years	48
6–10 years	60
>10 years	312
Total	420
Total cost ($) of treatment using EMI (Ci*Mi)	
2–5 years	92 063
6–10 years	239 746
>10 years	2 194 156
Total	2 525 965
Monthly cost ($) of comparator (Cc) using FEIBA	186 748
Mean duration (in months) for different patient age groups on FEIBA regimen (Mc)	
2–5 years	48
6–10 years	60
>10 years	192
Total	300
Total cost ($) of treatment using FEIBA (Cc*Mc)	
2–5 years	8 963 891
6–10 years	23 343 465
>10 years	131 470 395
Total	163 777 751
(Mi–Mc)/12 (in years)	10
Adjusted ICER ($) for India (ICERi)	Cost saving
Adjusted ICER (₹) for India (ICERi)*	Cost saving

*The exchange rate used was ₹82.25 for US$1, as of 15 May 2023.
FEIBA, factor eight inhibitor bypass activity; ICER, incremental cost-effectiveness ratio.

Discussion

Using different ICER adjustment methods, we found that emicizumab resulted in cost savings from the payers' perspective for both the vial strengths (30 and 150 mg/mL), but it did not appear to be cost-effective from the societal perspective. Using moderate adjustment method, implementing emicizumab prophylaxis demonstrated cost-saving potential from the health system perspective. Furthermore, emicizumab prophylaxis appeared to be cost saving using the complex adjustment method across different age groups from both the health system and societal perspectives. These findings highlight the potential value of emicizumab as a cost-saving approach for patients with haemophilia A in India and have implications for decision-making regarding its inclusion in the national health benefits package.

In addition to our source HTA report, it is important to note that multiple economic evaluation studies conducted in France, Korea and Italy consistently demonstrated the cost-effectiveness of emicizumab prophylaxis in patients with haemophilia A and inhibitors. For instance, a study conducted in France reported emicizumab as a dominant treatment option, saving €234 191 with a gain of 0.88 QALYs.[14] In Korea, the cost-utility analysis revealed that lifetime emicizumab prophylaxis prevented 807 bleeding episodes, extended 3.04 QALYs and reduced costs by $2.6 million.[17] Similarly, the Italian study found that emicizumab prophylaxis was more effective (0.94 QALYs) and cost saving (€19.4/€24.4 million per patient lifetime) compared with BPA prophylaxis.[13]

The above findings provide consistent evidence on emicizumab's potential for cost-effective prophylaxis in improving patient outcomes and reducing healthcare costs. It is essential to acknowledge that comparing the ICER estimates between these studies and the current study is challenging due to variations in study population, modelling techniques, assumptions and data sources. Nevertheless, the results of economic evaluations conducted in other settings support the potential cost-effectiveness of implementing

Table 4 Adjusted ICERs for emicizumab prophylaxis among patients with haemophilia A and inhibitors compared with those without prophylaxis in India using the complex adjustment method

Perspective and age group	Parameter	Emicizumab prophylaxis	No prophylaxis
Health system and <12 years	Adjusted cost ($)	2 862 245	4 291 604
	Adjusted QALYs	20.11	18
	Incremental adjusted cost ($)	−1 429 359	–
	Incremental adjusted QALYs	2.11	–
	ICER ($)	Cost saving	–
	ICER (₹)*	Cost saving	–
Health system and ≥12 years	Adjusted cost ($)	2 659 952	3 893 373
	Adjusted QALYs	13.6	12.79
	Incremental adjusted cost ($)	−1 233 421	–
	Incremental adjusted QALYs	0.8	–
	ICER ($)	Cost saving	–
	ICER (₹)*	Cost saving	–
Societal and <12 years	Adjusted cost ($)	2 935 463	4 386 074
	Adjusted QALYs	20.11	18
	Incremental adjusted cost ($)	-1 450 611	–
	Incremental adjusted QALYs	2.11	–
	ICER ($)	Cost saving	–
	ICER (₹)*	Cost saving	–
Societal and ≥12 years	Adjusted cost ($)	2 715 490	3 999 457
	Adjusted QALYs	13.6	12.79
	Incremental adjusted cost ($)	−1 283 966	–
	Incremental adjusted QALYs	0.8	–
	ICER ($)	Cost saving	–
	ICER (₹)*	Cost saving	–

*The exchange rate used was ₹82.25 for US$1, as of 15 May 2023.
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

emicizumab in the Indian context, as also signalled by the findings of the current study. However, it is crucial to estimate the budget impact of implementing emicizumab prophylaxis in India which will further inform policy decisions and determining its inclusion in the state or national benefits package.

In the study, various key parameters required for the ICER adjustment methods were obtained from the cost-effectiveness report published by the Institute for Clinical and Economic Review. This report served as a valuable data source for the majority of the essential parameters required in this study as the report used the same PICO framework as the one developed for the aHTA. This further supported the relevance and applicability of the obtained data. It is also important to note that the parameters reported in the Institute for Clinical and Economic Review's report were predominantly derived from the clinical evidence presented in the HAVEN trials, which ensured the inclusion of robust clinical effectiveness data for the ICER adjustments.

Certain patient-related parameters were collected from two expert haematologists specialising in the treatment of patients with haemophilia A and inhibitors at a tertiary care centre in India. This approach allowed for the inclusion of valuable insights from a clinician with direct experience in the Indian context. By incorporating parameters from the Institute for Clinical and Economic Review's report, and expert opinion, this study encompassed a comprehensive and reliable data for the analysis.

In the study, translating the findings from the US to the Indian context presented significant challenges and introduced uncertainties. As mentioned earlier, the majority of data related to cost-effectiveness, costs and QALYs required for the ICER adjustment were obtained from the full HTA report conducted in the USA by the Institute for Clinical and Economic Review. This introduces the inherent limitations of applying evidence derived from a different healthcare system and population to the Indian setting, along with the assumptions and limitations of each of our adjustment methods as noted above. Differences in healthcare practices, resource availability, disease epidemiology, treatment patterns and cost structures between the USA and India may impact the generalisability and applicability of the findings. Furthermore, the use of different pricing structures, inflation rates and cost variations across countries adds another layer of complexity in estimating the ICERa. These uncertainties should be considered when interpreting the results of this study regarding the implementation of emicizumab prophylaxis in India.

Our diverse team of six researchers, comprising both junior and senior members, successfully conducted this project while managing their other responsibilities, which reflects the real-world challenges of research. The project was completed within a 4-month time frame, with junior researchers dedicating approximately 60 hours each and senior researchers contributing around 20 hours each. Being our first implementation of the aHTA methodology, there was a significant learning curve in planning and executing the research, resulting in the time and duration required for completion. However, with subsequent studies, we anticipate improved efficiency as we leverage our growing expertise. By sharing these insights, we aim to inform readers about the practical considerations, resource requirements and potential for optimisation associated with aHTA studies, promoting their adoption in different country settings.

Strengths and limitations

The strength of this study lies in its uniqueness, methodological rigour, efficient resource utilisation and rapidity in decision-making. As the first study of its kind in India, it provides valuable insights into the cost-effectiveness of emicizumab prophylaxis for patients with haemophilia A and inhibitors. Expanding on the aHTA methodologies, we presented the feasibility of using this approach for rapid HTA assessments in the Indian context by generating timely cost-effectiveness evidence for informed decision-making for policymakers and healthcare professionals.

The efficient utilisation of resources, including manpower and time, further contributes to the study's strengths. Active involvement of stakeholders, including clinicians, at every step of the study improved its relevance and applicability. Additionally, the research question itself was suggested by a clinician, enhancing its direct connection to real-world clinical practice.

The RES methodology used in the study allowed rapid assessment of available evidence in a short time frame, which aligned with the principles of undertaking an aHTA methodology, to provide evidence for any urgent policy decision. Further, the approach of consultations with experts facilitated synthesising evidence from seminal work on the topic and facilitated the judgement on the applicability of the evidence to the Indian settings. These strengths inherent to the RES methodology, combined with

the study's findings, could inform policy deliberations and facilitate the uptake of emicizumab prophylaxis within the Indian healthcare system.

The study also has certain limitations. We acknowledge that this aHTA methodology represents a novel approach, and the methodologies employed in aHTA studies can significantly vary across different settings. This uniqueness presents certain limitations but is balanced by the strengths of the RES and ICER adjustment methods employed in the study. The ICER adjustment methods are also novel and exploratory, and are based on an understanding of key health system factors that differ by setting, such as intensity of resource utilisation, life expectancy, health system costs and technology prices. These formulae have not yet been validated, in part because there is no natural counterfactual de novo economic evaluation conducted in the country of interest. Further work is required to validate their use and confirm their benefit.

Key parameters such as mean duration of treatment, drug costs, life expectancy and bleeding episodes relied on expert opinion, which introduces uncertainty into the estimates. This is mainly due to a lack of Indian-specific evidence from primary studies on emicizumab including randomised controlled trials, potentially impacting the generalisability of the findings.

The ICER adjustments are presented in deterministic fashion in this study and do not carry any quantitative presentation of uncertainty that might have been included in the source HTA report. This may prove to be a challenge if the source estimates are themselves deterministic in nature. If probabilistic estimates are available then adjusted CIs and other quantitative estimates could be generated in future aHTA iterations. In addition, the results of sensitivity analyses conducted in the source report could be adjusted to the local context, and limited sensitivity analyses (eg, price, life expectancy) might even be calculated after local adjustment.

Another limitation is the focus on the reduction in annualised bleeding rates as the primary outcome. Secondary outcomes, such as rates of treated bleeds and treatment for surgical bleeds, were not considered in the analysis, limiting the comprehensive inclusion of the treatment's effectiveness. We lacked the resources for a de novo CEA, and did not conduct a budget impact analysis, which would have provided insights into the financial implications of implementing emicizumab prophylaxis in India.

Methodological limitations in the trials of emicizumab should be acknowledged as various key parameters for the analysis were taken from these. These include the relatively short follow-up duration and lack of head-to-head randomised comparisons with BPAs. Furthermore, the safety of emicizumab in various clinical settings has not been extensively evaluated, which may affect the understanding of its risk-benefit profile. It is important to consider these limitations when interpreting the study findings.

From the methodological front, the RES approach employed could have introduced selection bias, as the expedited nature of RES might not have captured the entirety of existing evidence before commencing the evidence synthesis process. However, it is worth emphasising that the study's iterative process for acquiring evidence, coupled with periodic consultations with experts in the field, could have helped to mitigate this bias.

This study on cost-effectiveness of emicizumab for patients with inhibitors provides valuable lessons for future research and decision-making. Limited availability of full HTA reports underscores the need for more comprehensive evidence generation. Although the RES approach could be considered a pragmatic and efficient way to provide timely decision-making, it comes with a trade-off between comprehensiveness and risk of bias which needs to be considered while interpreting the findings. Further, the absence of cost-effectiveness studies from Indian or Asian settings restricted generalisability of study findings. The lack of primary data on treatment costs highlights the importance of data availability in India. These lessons underscore the need to address data gaps, promote research activities and enhance the availability of robust evidence for informed decision-making.

Conclusion

The findings of the ICERa from this study suggest the potential cost-effectiveness of implementing emicizumab prophylaxis in India for patients with haemophilia A with inhibitors, and the feasibility of using aHTA methods for rapid evidence generation to inform time-sensitive decision-making in India. However, future studies should address the limitations described earlier to strengthen the evidence base on the cost-effectiveness of emicizumab prophylaxis in the Indian context. Additionally, conducting a full HTA on the topic that includes patients with haemophilia with inhibitors, and a comprehensive budget impact analysis are crucial to inform policy decisions in the long term regarding the implementation of emicizumab prophylaxis in India and its funding through public financing.

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Contributors SSK, AM and DO conceptualised the study. PS, VR and AM curated the data. PS and VR conducted the formal analysis. Validation involved SSK, DO, AM and KT. PS, VR and SSK wrote the original draft, while all authors contributed to reviewing and editing. All authors read and approved the final version of the manuscript. SSK is responsible for the overall content as guarantor.

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Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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Supplementary file

Topic Selection:

A clinician from a centrally funded tertiary care hospital in India suggested the topic of interest. Initially, we requested the clinician to provide the research question in the widely recognized PICO (Population, Intervention, Comparator, Outcome) framework. To evaluate scope and relevance of the research question to the Indian context, we conducted a targeted literature review to assess whether the PICO components aligned with the intervention, available international evidence, and clinical practices in India. After the review, we determined the components for this aHTA study as described in the manuscript.

Step 1: Topic prioritization

Expert consultations emphasized the growing interest among Indian states, such as Punjab, in making Emicizumab available in public hospitals. Additionally, literature search and expert inputs revealed promising results from large randomized trials and highlighted the potential benefits of introducing Emicizumab in the Indian healthcare system. Moreover, the inclusion of hemophilia under the 'Rights of Persons with Disabilities Act' by the Government of India underscored the importance of addressing this research question to alleviate the burden of disability (See Supplementary Table 2). These considerations reinforced the necessity of conducting an aHTA and led us to select this topic for further assessment within the Indian context.

Kar SS, *et al. BMJ EBM* 2024;0:1–9. doi: 10.1136/bmjebm-2023-112492

Supplementary table 1: PICO elements for the study

PARAMETERS	
Population	Hemophilia A patients with inhibitors
Intervention	Emicizumab prophylaxis
Comparator	No prophylaxis
Outcomes	a) Reduction in Annualised bleed rates b) Reduction in all bleeds (treated and untreated), treated spontaneous bleeds, treated joint bleeds, and treated target joint bleeds, c) Improved Quality of life
Price	Rs.58,900 for 30 mg/ml Rs. 294,392 for 150 mg/ml
Available evidence on value proposition (e.g., cost-effectiveness, other benefits)	We have two relevant reports (ICER, CADTH), 3 cost-effectiveness studies conducted in Korea, France and Italy stating the cost-effectiveness of emicizumab and recommending emicizumab prophylaxis. Haven's clinical trial 1,2,4 &5 have thrown light on the clinical benefits of emicizumab prophylaxis.
Expected uptake and utilisation	If available, the expected uptake and utilization is to be around 90%-100% based on expert opinion
Ethical, patient, and social considerations	The study focuses on a population that is considered to be vulnerable. It calls for special attention on addressing the ethical patient and social considerations.
Laws, statues, or policies that may impact technology use in India	Haemophilia has been listed by GoI under the list of disabilities under The Rights of Persons with disabilities Act . Under this act *"responsibility has been cast upon the appropriate governments to take effective measures to ensure that the persons with disabilities enjoy their rights equally with others"*.
Justification for consideration of the topic as high priority	Clinical experts reiterated that a lot of the patients live in rural and remote areas. Parents can administer Emicuzimab subcutaneously to their children at home (either once fortnightly or monthly). Emicizimab has tremendous advantage in terms of cost compared incurred by patients receiving on demand treatment. It significantly reduces the travel cost, days away from work, and school days missed. The increase in compliance prevents bleeds and complications, and causes gains in functional, productive life, and duration of life.
Feasibility considerations (e.g., training and certification)	Administering emicizumab might not necessitate any sort of training or certification. Hence its feasible to provide emicizumab at a primary healthcare level too.

Protocol used for the Rapid evidence synthesis:

1. Title: Clinical and economic evidence on the Emicizumab Prophylaxis for Hemophilia A with Inhibitors: A rapid evidence synthesis
2. Review questions: We formulated the key questions by considering pivotal factors highlighted in prior research and discussions with stakeholders. For each of these questions, our initial approach will involve searching for pre-existing compilations of evidence syntheses. 1) What is the evidence for the impact of emicizumab for key clinical outcomes among Hemophilia A patients with inhibitors compared to no prophylaxis? **2)** What is the cost-effectiveness evidence for emicizumab prophylaxis compared to standard care (no prophylaxis) for Hemophilia A patients with inhibitors?
3. Objective: To assess the clinical and economic evidence on the Emicizumab Prophylaxis for patients with Hemophilia A with Inhibitors using the rapid evidence synthesis approach
4. Eligibility criteria: ***Population:*** Hemophilia A patients with inhibitors irrespective of any age group ***Intervention:*** Emicizumab prophylaxis ***Comparator:*** No prophylaxis ***Outcomes:***

A) Clinical outcomes: Reduction in annualized bleed rates (ABR), Reduction in all bleeds (treated and untreated), treated spontaneous bleeds, treated joint bleeds, and treated target joint bleeds, Improved quality of life

B) Economic outcomes: QALY, and ICERs

5. Studies that are peer reviewed studies/reports published in English language, conducted among human subjects and when full texts are available will be included for the review.

6. **Types of study to be included:** The review will include various types of study designs—randomized controlled trials (RCTs), cost-effectiveness analyses (CEA) studies and HTA reports, systematic reviews (including rapid reviews). We will also incorporate qualitative and mixed methods reviews alongside quantitative ones, provided they had a well-documented search strategy and explicit inclusion criteria. In the absence of existing evidence syntheses for specific inquiries, results, or particular groups under investigation, we will consider observational studies as well.

7. **Information sources:** Searches will be conducted for literature published from 1 Jan 2010 to 31 May 2023. The search will be conducted across the PubMed (MEDLINE) database, and Cochrane Database of Systematic Reviews, and several healthcare technology assessment (HTA) registries including INAHTA, NICE, CADTH, HITAP, PBAC/MSAC, PHARMAC, ICER.IECS, CONITEC, the Philippine HTA Unit, MAHTAS, ACE, INEAS, C2H, NECA, Tufts CEA registry, and the York database. Additionally, we will employ citation scanning techniques, especially when identifying comprehensive reviews.

8. **Data extraction (selection and coding)**

Study selection will be conducted in two steps. Firstly, all the articles sourced will be collated, and duplicates will be removed using Zotero (version 5.0). Two reviewers will independently screen the title and abstract of each study against the eligibility criteria using a web-based

application, 'Rayyan' and the full text of all eligible studies will be retrieved. In the second step, full text articles will be reviewed against the eligibility criteria concerning inclusion criteria and the study outcomes. Those articles/reports that satisfied the criteria will be selected for the review. In both steps, disagreements between the reviewers during the selection process were resolved through consensus or with the help of another reviewer. During the full text review, attention was given to RCTs, cost-effectiveness studies / HTA reports published by reputed organizations for inclusion in this review. We will also consult clinical experts treating Hemophilia A patients to gather any additional evidence on the topic.

9. **Data charting process:** Data extraction will be carried out by two reviewers independently. Data extraction from full-text studies will be carried out using a data extraction form developed in Microsoft Excel 2019 (Microsoft Corporation). The data extracted will be reviewed for accuracy and completeness by another reviewer. Any discrepancy will be resolved through consensus or referral to another reviewer. Whenever information under any field in the data extraction sheet is missing, it will be mentioned as either as 'not reported' or 'not applicable'.

10. Data items:

During the full-text review phase of the sourced article / review, various data types that will be extracted are listed below. Data will be extracted into three main domains: Background Information, Clinical Evidence, and Cost-effectiveness Data.

1. Background Information:

a. Demographic and contextual details, including study country, analysis type, title, author/s, and date of publication.

b. Characteristics of the study population, such as demographic information.

c. Information related to the study's intervention, comparators, and funding sources.

2. Clinical Evidence:

a. Specifics regarding the study design (type of study).

b. Qualitative comments on clinical benefits observed in the study.

c. Quantitative outcomes measured, along with associated measures of variance.

d. Statistical significance, as indicated by p-values.

e. Limitations, critiques, and any residual uncertainties regarding the clinical evidence.

f. Safety-related evidence considered in the study.

3. Cost-effectiveness Data:

a. Cost-related information, including intervention costs, comparator costs, and incremental costs.

b. Quality-Adjusted Life Years (QALYs) associated with the intervention, comparator, and incremental QALYs.

c. Cost-effectiveness threshold used in the study.

d. Recommendations or conclusions drawn from the cost-effectiveness analysis.

e. Generalizability concerns or any other uncertainties related to the cost-effectiveness data.

11. Risk of bias (quality) assessment

As this review follows Rapid Evidence Synthesis methodology, risk of bias assessment will be not be conducted for the studies chosen for data extraction. Further, it is important to note that only those studies/reports on the topic which have been prepared by reputed organizations will be chosen for data extraction. This is because RES approach does not require statistical quantitative synthesis from various evidence sources for any particular input parameter and necessitates only reliable estimate from any reliable source.

12. Strategy for data synthesis:

We will provide two levels of simplified summaries for the evidence that's been extracted. The first level will give a concise overview of the overall evidence supporting the clinical significance and cost effectiveness of emicizumab prophylaxis for individuals with hemophilia A who have developed inhibitors. The second level offers a concise, bulleted summary assessing the certainty and significance of the evidence for each component.

13. Search Queries for PubMed Search

a. Clinical evidence

((((((((((("Hemophilia A"[Mesh]) OR "Factor VIII"[Mesh])) OR "Blood Coagulation Disorders"[Mesh]) AND "Diagnosis"[Mesh]) OR "Disease Management"[Mesh]) OR "Quality of Life"[Mesh]) OR "Treatment Outcome"[Mesh]) OR ("Factor VIII inhibitors" [All Fields] OR "Prophylaxis" [All Fields])) AND (((((("Randomized Controlled Trial" [Publication Type])) OR "Non-Randomized Controlled Trials as Topic"[Mesh]) OR "Pragmatic Clinical Trial" [Publication Type]) OR "Cohort Studies"[Mesh]) OR "Single-Case Studies as Topic"[Mesh]) OR "Clinical Trial" [Publication Type])) AND ("By passing agents [All Fields]" OR" factor VIII [All Fields]" OR "standard of care[All Fields]")) AND (Emicizumab)

b. Economic Evaluation

((((((((((((((((((((((((cost-benefit analysis[MeSH Terms]) OR (cost-effectiveness analysis[MeSH Terms])) OR (decision trees[MeSH Terms])) OR (cost util*[Title/Abstract])) OR (cost-benefit*[Title/Abstract])) OR (cost-effect*[Title/Abstract])) OR (cost-min*[Title/Abstract])) OR (cost-min*[Title/Abstract])) OR (cost-consequence*[Title/Abstract])) OR (economic evaluation*[Title/Abstract])) OR (economic assessment*[Title/Abstract])) OR (economic analys*[Title/Abstract])) OR (health technolog*[Title/Abstract]))) OR (markov chains[MeSH Terms])) OR (monte carlo method[Title/Abstract])) OR (Decision Theory[Title/Abstract])) OR (economic model*[Title/Abstract])) OR (markov*[Title/Abstract])))) OR (return on investment[Title/Abstract])) OR (comparative assessment*[Title/Abstract])) OR (budget impact

<table>
<tr><td colspan="2">analysis[Title/Abstract])) OR ("cost*"[All Fields] OR "expenditure*"[All Fields] OR "cost analysis*"[All Fields] OR "burden"[All Fields] OR "economic*"[All Fields] OR "assets"[All Fields] OR "direct cost*"[All Fields] OR "Illness cost*"[All Fields] OR "Sickness cost*"[All Fields] OR "Cost of sickness"[All Fields] OR "economic burden"[All Fields] OR "short term"[All Fields] OR "long term"[All Fields])) OR ((((((((("Cost of Illness"[Mesh]) OR "Costs and Cost Analysis"[Mesh]) OR "Economics"[Mesh]) OR "Cost-Benefit Analysis"[Mesh])) OR "Cost-Effectiveness Analysis"[Mesh]) OR "Health Care Costs"[Mesh]) OR "Health Expenditures"[Mesh]) OR "Direct Service Costs"[Mesh]) OR "Hospital Costs"[Mesh]) OR "Models, Economic"[Mesh]))) AND ("Emicizumab")</td></tr>
<tr><td colspan="2">Language: English, Free full text, human studies</td></tr>
<tr><td>2. Registries and database</td><td>Key terms used</td></tr>
<tr><td>a) INAHTA Database: https://database.inahta.org/</td><td rowspan="8">Emicizumab – Hemlibra, emicizumab-kxwh,emicizumab

Hemophilia-Hemophilia A, Congenital Hemophilia A, Factor VIII Deficiency, Congenital, Factor 8 Deficiency, Congenital, Classic hemophilia.

Economic evaluation- Cost effectiveness analysis, cost effectiveness ratios, Cost and cost analysis</td></tr>
<tr><td>b) NICE: https://www.nice.org.uk/</td></tr>
<tr><td>c) CADTH: https://www.cadth.ca/</td></tr>
<tr><td>d) HITAP: https://www.hitap.net/en/</td></tr>
<tr><td>e) PBAC/MSAC: https://www.health.gov.au/topics/health-technologies-and-digital-health/health-technology-assessments</td></tr>
<tr><td>f) PHARMAC: https://pharmac.govt.nz/</td></tr>
<tr><td>g) ICER: https://icer.org/</td></tr>
<tr><td>h) IECS: https://www.iecs.org.ar/en/</td></tr>
</table>

i) CONITEC: https://www.gov.br/conitec/pt-br	
j) Philippine HTA Unit: https://hta.doh.gov.ph/	
k) MAHTAS (https://www.moh.gov.my/)	
l) ACE (https://www.ace-hta.gov.sg/)	
m) INEAS (https://www.ineas.tn/)	
n) C2H (https://c2h.niph.go.jp/en/),	
o) NECA (https://www.neca.re.kr/eng/index.do;jsessionid=644D6D2DD8A7F0073FA269BD13F97BF5)	
p) Tufts CEA Registry: https://cear.tuftsmedicalcenter.org/	
q) York Databases: https://www.crd.york.ac.uk/CRDWeb/	
r) Cochrane: https://www.cochranelibrary.com/	

Supplementary table 2: Background information

BACKGROUND									
Country	**Analysis type**	**Link**	**Title**	**Author**	**Date**	**Population**	**Intervention**	**Comparator(s)**	**Funding source**
HTA Reports									
CANADA (CADTH Report)	CEA	https://www.cadth.ca/sites/default/files/hta-he/ob0005-emicizumab-eeconomic-report.pdf	Hemlibra (Emicizumab): Economic Review Report	CADTH (Canadian Agency for Drugs and Technologies in Health)	Sep-19	HAVEN CLINICAL TRIAL	Emicizumab	BPA prophylaxis, BPA on demand	CADTH
USA (ICER report)	CEA	https://icer.org/wp-content/uploads/2020/10/ICER_Hemophilia_Final_Evidence_Report_041618.pdf	Emicizumab for Hemophilia A with Inhibitors: Effectiveness and Value	Institute for clinical and economic review	Apr-18	Adolescents and adults (ages 12 and older) • Children (under 12 years)	Emicizumab for prophylaxis.	No prophylactic therapy Prophylaxis with a BPA	ICER
Cost effectiveness studies									
Italy	CEA and Budget impact analysis	https://doi.org/10.1055/s-0039-3401822	Cost-Effectiveness and Budget Impact of Emicizumab Prophylaxis in Haemophilia A Patients with Inhibitors	Cortesi PA et.al.	30.12.2019	Hemophilia A with inhibitors ≥ 4 years and older who failed ITI from the Italian NHS point of view.	Emicizumab	Bypassing agents	Roche Italy Spa
France	CEA	https://doi.org/10.1111/hae.14129	Cost-effectiveness of emicizumab vs bypassing agents in the prevention of bleeding episodes in haemophilia A patients with anti-FVIII inhibitors in France	Benoît Polack et.al	18.11.2020	≥ 12 years with congenital hemophilia A, history of a high titer of factor VIII inhibitor (≥5 Bethesda units per milliliter), Receiving episodic or prophylactic treatment with bypassing agents.	Emicizumab	Bypassing agents	Roche SAS, France

Korea	CEA	https://doi.org/10.1111/hae.14143	Cost-utility analysis of emicizumab prophylaxis in haemophilia A patients with factor VIII inhibitors in Korea	Hankil Lee et. al.	7.9.2020	≥ 12 years with congenital hemophilia A, history of a high titer of factor VIII inhibitor (≥5 Bethesda units per milliliter), Receiving episodic or prophylactic treatment with bypassing agents.	Emicizumab	Bypassing agents	JW Pharmaceuticals (grant number 2018-11-0268)
Clinical evidence									
HAVEN 1 Multicentric (43 centres)	Clinical trial	DOI: 10.1056/NEJMoa1703068	Emicizumab Prophylaxis in Hemophilia A with Inhibitors	Johannes Oldenburg	31-08-2017	≥ 12 years with congenital hemophilia A, history of a high titer of factor VIII inhibitor (≥5 Bethesda units per milliliter), Receiving episodic or prophylactic treatment with bypassing agents.	Subcutaneous emicizumab prophylaxis at a dose of 3.0 mg per kg of body weight weekly for 4 weeks. Followed by 1.5 mg per kilogram weekly (Group A)	No prophylaxis (Group B) BPA on demand	La roche
HAVEN 2 Multicentric (27 centres)	Clinical trial	https://doi.org/10.1182/blood-2018-99-118153	Emicizumab Prophylaxis Provides Flexible and Effective Bleed Control in Children with Hemophilia A with Inhibitors: Results from the HAVEN 2 Study	Guy Young	19-10-2018	PwHA with inhibitors aged <12 years (or 12-17 years if <40kg) previously treated with episodic or prophylactic bypassing agents (BPAs) to receive emicizumab prophylaxis for ≥52 weeks	A loading dose of 3mg/kg emicizumab was given QW for 4 weeks followed by a maintenance dose of 1.5mg/kg QW, 3mg/kg Q2W or 6mg/kg Q4W	Three groups varied by maintenance dose (1.5mg/kg QW, 3mg/kg Q2W or 6mg/kg Q4W)	La roche

HAVEN 2 Multicentric (27 centres)	QOL assessment	https://doi.org/10.1111/hae.14183	Health-related quality of life and caregiver burden of emicizumab in children with haemophilia A and factor VIII inhibitors—Results from the HAVEN 2 study	Maria Elisa Mancuso	21-10-2020	Paediatric PwHA <12 years of age, with FVIII inhibitors, who were receiving episodic or prophylactic treatment including FVIII (long- and short-acting) and BPAs (activated prothrombin complex concentrate [aPCC] or recombinant activated FVII [rFVIIa]) were eligible to participate.	QOL assessment from baseline to 49 weeks (baseline, 13, 25,37,49 weeks) Baseline Haemo-QoL SF II for children Adapted Inhibitor-QoL questionnaire for care givers		F. Hoffmann-La Roche Ltd. and Chugai Pharmaceutical Co., Ltd.
HAVEN 4 Multicentric	Clinical trial	https://doi.org/10.1016/S2352-3026(19)30054-7	Efficacy, safety, and pharmacokinetics of emicizumab prophylaxis given every 4 weeks in people with haemophilia A (HAVEN 4): a multicentre, open-label, non-randomised phase 3 study	Wipe WS et. al.	16.04. 2019	≥ 12 years with congenital hemophilia A, history of a with or without inhibitors, Receiving episodic or prophylactic treatment with bypassing agents.	Profile of emicizumab given as a loading dose of 3 mg/kg weekly for 4 weeks, followed by a maintenance dose of 6 mg/kg every 4 weeks in an expansion cohort upto 25 weeks.		F Hoffmann-La Roche and Chugai Pharmaceutical.

HAVEN 5 Multicentric	Clinical trial	https://doi.org/10.1002/rth2.12670	Prophylactic emicizumab for hemophilia A in the Asia-Pacific region: A randomized study (HAVEN 5)	Yang MD et al	Feb 2022	Individuals aged ≥12 years with severe hemophilia A without factor VIII (FVIII) inhibitors, or hemophilia A of any severity with FVIII inhibitors, across the Asia-Pacific region.	Participants were randomly assigned (2:2:1) to receive emicizumab 1.5 mg/kg once weekly (arm A), emicizumab 6 mg/kg every 4 weeks (arm B), or no prophy-laxis (arm C).		F Hoffmann-La Roche and Chugai Pharmaceutical

Supplementary table 3: Clinical evidences

Clinical Evidence								
Study name	**Type of study**	**Comments on clinical benefit**	**Outcome**	**Measure of variance**	**P-value**	**Limitations, critiques, and residual uncertainties regarding the clinical evidence**	**Safety evidence**	**Other considerations**
HTA Reports								
CADTH report's clinical data was based on HAVEN 1 trial	RCT	Emicizumab prophylaxis dominated BPA prophylaxis; i.e., emicizumab was associated with lower total costs and higher QALYs	The utility values for emicizumab and on-demand treatment were obtained from the HAVEN 1 clinical trial. Utilities for prophylaxis with BPAs were					

			sourced from the NIS					
ICER Report clinical data was based on HAVEN's trial 1 & 2	RCT	Given the results of the trials and the reduced burden with emicizumab, for children younger than 12 we have high certainty that emicizumab provides at least a small net health benefit ("B+") compared with no prophylaxis, and in adults and children we have high certainty that emicizumab provides at least a small health benefit ("B+") compared with prophylaxis with BPAs. The randomized HAVEN 1 trial found that prophylaxis with emicizumab substantially reduced bleeding events in adolescents and adults (ages 12 years and older) compared to no prophylaxis, and also compared to prior	Emicizumab resulted in fewer bleed events (total bleeding events, treated bleeding events , treated joint bleeding and treated target joint bleeding), higher QALYs, and lower total costs relative to no prophylaxis and to prophylaxis with BPAs over a lifetime time horizon from both the health system and societal perspectives. Measures on pain and mortality were also comparatively lower in the intervention group			*The study lacked long-term safety data, and it is possible that so-far undetected toxicities and adverse events will be encountered over time *Patients may have been more adherent to therapy which would tend to make emicizumab appear more effective than BPAs. *While we modeled a decrease in joint damage with reduced bleeding, we assumed no reduction in mortality, given the lack of data. If reductions in bleeding with prophylaxis correlate with reduction in mortality, the relative benefit with emicizumab will be larger than estimated in our modeling *We have only observational data *The safety of emicizumab has not been evaluated in many clinical settings. *Long-term outcomes were not measured in the trials of emicizumab.	*An increased risk of thrombotic microangiopathy and thrombotic events were observed in patients on emicizumab who received large and multiple doses of aPCC for treatment of bleeding events *The safety of emicizumab in patients experiencing events such as sepsis or major trauma, has not been assessed. We also have more limited evidence on safety in patients younger than age 12 than in older patients.	

		prophylaxis with BPAs. Interim results from the single-arm HAVEN 2 trial indicated that prophylaxis with emicizumab prevented bleeding events in most children; a substantial improvement was observed with emicizumab when compared to prior prophylaxis with BPAs Compared with no prophylaxis, emicizumab also improved health-related quality of life and caregiver burden						
Cost- effectiveness studies								
Cost-Effectiveness and Budget Impact of Emicizumab Prophylaxis in Haemophilia A Patients with	CEA		HAVEN 1 trial ABR with emicizumab (3.3 [95% CI, 1.3–8.1] whereas BPA had ABR-7.9 AS PER aPCC trials Utility score=0.72 for emicizumab prophylaxis for					

Inhibitors in Italy			the baseline and gradually improved over the 5 weeks . BPA also shows improvement in scores but that's not measured by EQ-5d-5l					
Cost-effectiveness of emicizumab vs bypassing agents in the prevention of bleeding episodes in haemophilia A patients with anti-FVIII inhibitors in France	CEA		HAVEN 1 trial outcome data					
Cost-utility analysis of emicizumab prophylaxis in haemophilia A patients with factor VIII inhibitors in Korea	CEA		HAVEN 1 trial for Emicizumab BPA: Korean data on ABR. ABR of patients with emicizumab prophylaxis was calculated using an 87% reduction rate from the HAVEN 1 trial, resulting in 6.1 per year					

Clinical evidence								
Haven trial 1	HAVEN Trial 1 phase 3 open-label, multicenter	ABR had a significant difference of 87% in favor of emicizumab prophylaxis, Significant differences in favor of emicizumab prophylaxis were also observed in all secondary bleeding-related end points: events of spontaneous bleeding, joint bleeding, and target joint bleeding as well as all bleeding events Improvements in EQ-VAS and EQ-5D-5L IUS with emicizumab prophylaxis were seen as early as week 5, maintained through week 25. In the no prophylaxis group (Arm B), EQ-VAS and EQ-5D-5L IUS scores remained near baseline levels or decreased slightly during the study.	The annualized bleeding rate was 2.9 events (95% CI: 1.7 to 5.0) with emicizumab prophylaxis (group A) versus 23.3 events (95% CI, 12.3 to 43.9) with no prophlaxis (group B), For Treated spontaneous bleeds ABR- 1.3 (0.73, 2.19) for group A & 16.8 (9.94, 28.30) for group B For treated joint bleeds ABR- 0.8 (0.26, 2.20) for group A & 6.7 (1.99, 22.42) for group B For treated target joint bleeds ABR-0.1 (0.03, 0.58) for group A& 3.0 (0.96, 9.13) for group B Zero bleeds- 62.9% (44.9, 78.5) for group A	Change in: Annualised bleed rates for treated bleeds, all bleeds (treated and untreated), treated spontaneous bleeds, treated joint bleeds, and treated target joint bleeds, QOL				

			& 5.6% (0.1, 27.3) for group B All bleeds ABR-5.5 (3.58, 8.60) for group A, 28.3 (16.79, 47.76) for group B Using Haem-O-Qol the mean change in total score of QOL at 25 week was −10.7 (−16.5, −4.8) for group A, 2.5 (−2.5, 7.4) for group B					
HAVEN Trial 2	HAVEN Trial 2	Emicizumab prophylaxis is well tolerated and can prevent or substantially reduce bleeds in this population	ABR: QW: 0.3 (0.17-0.50), Q2W 0.2 (0.03-1.72), and Q4W 2.2 (0.69-6.81) Zero treated bleeds: QW: 76.9%, Q2W:90%, Q4W: 60%	Annualized bleed rates, Zero treated bleeds				
HAVEN Trial 2 (Qol assessment)	Longitudinal study	Prophylactic emicizumab produced substantial and sustained improvements in HRQoL of paediatric PwHA with FVIII	QOL among: 1. Children: Baseline: 30.2 (14.9) 49 weeks: 23 (13.9) Caregivers: Baseline: 24.5 (29.8)	Change in QOL among: Children: -9.6 Caregivers: -6.4				

		inhibitors and their caregivers	49 weeks: 16.3 (23.7)					
Haven 4 Trial	Haven 4 Trial	Emicizumab given once every 4 weeks showed clinically meaningful bleed control while being well tolerated. This regimen could improve patient care by decreasing treatment burden and increasing adherence to effective prophylaxis, potentially decreasing the development of secondary complications for people with haemophilia A.	Annualised rate of treated bleeds was 2·4 (95% CI 1·4–4·3). 23 (56·1%; 95% CI 39·7–71·5) of 41 reported no treated bleeds and 37 (90%; 76·9–97·3) reported zero to three treated bleeds. The annualised bleed rate was 4·5 (95% CI 3·1–6·6) for all bleeds, 0·6 (0·3–1·5), for treated spontaneous bleeds, 1·7 (0·8–3·7) for treated joint bleeds, and 1·0 (0·3–3·3) for treated target joint bleeds	Annualised bleed rates for treated bleeds, all bleeds (treated and untreated), treated spontaneous bleeds, treated joint bleeds, and treated target joint bleeds				
Haven 5 Trial	Haven 5 Trial	Emicizumab was administered 3 mg/kg once weekly for the first 4 weeks (loading dose)followed by a maintenance dose	Following emicizumab prophylaxis, the model-based ABR (95% CI) for treated bleeds was 1.0 (0.53-	The primary efficacy end point was annualized bleeding rate (ABR) for treated bleeds in people with hemophilia A receiving once-weekly				

		of either 1.5 mg/kg once weekly (arm A) or 6 mg/kg every 4 weeks (arm B), or no prophylaxis (arm C) (Figure 1). After completing 24 weeks of study, participants randomized to arm C could switch to emicizumab (3 mg/kg once weekly loading dose for 4 weeks followed by a maintenance regi-men of 6 mg/kg every 4 weeks). After at least 24 weeks of emici-zumab prophylaxis, participants could continue taking maintenance therapy (1.5 mg/kg once weekly or 6 mg/kg every 4 weeks) or, if they had suboptimal control of bleeding, defined as ≥2 spontaneous and clinically significant bleeding events during the prior 24 weeks	1.85) for arm A and 1.0 (0.50-1.84) for arm B, compared with 27.0 (13.29-54.91) for arm C. Therefore, a statistically significant and clinically meaningful reduction of 96% in ABR for treated bleeds was observed for both emicizumab once weekly and every 4 weeks compared with no prophylaxis (both P < .0001;	or every-4-weeks emicizumab prophylaxis or no prophylaxis (see Appendix S1 for definition of treated bleeds). Secondary efficacy end points were ABRs for all bleeds and treated spontaneous/joint/target joint bleeds in participants receiving once-weekly or every-4-weeks emicizumab prophylaxis versus no prophylaxis.				

		of emicizumab administration, both occurring after the end of the loading-dose period, change to an increased dose of 3 mg/kg once weekly.						

Supplementary table 4: Cost effectiveness data

Cost-Effectiveness								
Intervention costs	**Comparator costs**	**Incremental costs**	**Intervention QALYs**	**Comparator QALYs**	**Incremental QALYs**	**Cost-effectiveness threshold**	**Recommendation or conclusion**	**Generalizability concerns or other uncertainties**
HTA reports- CADTH Report								
Emicizumab: 32,574,676	BPA Prophylaxis: 88,227,298 On Demand: 19,814,261	Manufacturer: Emicizumab vs. BPA Prophylaxis: $ -55,652,622, Emicizumab vs. BPA On-Demand: $ 12,760,415 CADTH reanalysis: Emicizumab vs. BPA Prophylaxis	Manufacturer: Total QALY: Emicizumab: 31.476	Manufacturer: Total QALY: BPA Prophylaxis: 24.078 BPA On-Demand: 22.496	Manufacturer: Emicizumab vs. BPA On-Demand: 8.966 Emicizumab vs. BPA Prophylaxis: 7.385 CADTH reanalysis: Emicizumab vs. BPA On-Demand: 8.873 Emicizumab	$50,000 per QALY Cost-effectiveness (ICUR): Manufacturer: Emicizumab vs. BPA On-demand: 1,420,982 Emicizumab vs. BPA Prophylaxis: Dominates CADTH reanalysis:	In the inhibitor population, emicizumab is the dominant treatment compared with BPA prophylaxis, but, compared with on-demand BPA, emicizumab would require a price reduction 42% to be cost-effective	1.An unconventional modelling approach was used that included only two health states, alive and dead. Disease-related events (such as bleeding and arthroplasty), and their impact on quality of life (utility), were absorbed within the alive health state and were not explicitly defined as health states in the model 2. The use of treatment-specific utilities is discouraged as the cumulative effect of bleeding events (such as arthropathy) was not reflected in the model i.e. more transparent approach is to assign utility values to clinically relevant health states, per CADTH guidelines. 3. The dynamic change in inhibitor profile in the pediatric population (i.e., patients with pediatric hemophilia A receiving

		: $ – 49,403,244 Emicizumab vs. BPA On-Demand: $ 12,800,583			vs. BPA Prophylaxis: 7.384	Emicizumab vs. BPA On-Demand: 1,442,642 Emicizumab vs. BPA Prophylaxis: Dominates		emicizumab that go on to not develop inhibitors) was not included in the manufacturer's submission. Given the design of the model, it was not possible to address these structural limitations 4. Estimate of relative treatment effect: There is lack of head-to-head randomized evidence comparing emicizumab prophylaxis with BPAs prophylaxis. The manufacturer used an unpublished, observational, single-arm, NIS to estimate bleeding rates in patients receiving BPA prophylaxis. This lower-quality, non-randomized evidence is used alongside and directly compared with randomized trial data for emicizumab prophylaxis and on-demand BPA (HAVEN 1 study). The manufacturer also conducted a systematic review and identified one study4 comparing BPA prophylaxis with on-demand BPA; however, this study was only used in a sensitivity analysis. 5. Mortality: The manufacturer assumed that patients receiving on-demand BPA experience an SMR of severe hemophilia A throughout their lifetime, whereas patients receiving emicizumab or BPA prophylaxis experience SMR of mild-to-moderate hemophilia A. While the clinical expert consulted by CADTH considered this mortality benefit of prophylaxis to be plausible, it was noted that no evidence was provided by the manufacturer to support this assumption. 6. Arthroplasty assumptions: The manufacturer assumed that patients on prophylactic emicizumab or BPA would not

								require an arthroplasty due to reduced risk of bleeding, whereas patients receiving on-demand BPA would require an arthroplasty every 15 years (at ages 25, 40, 55, and 70, resulting in four arthroplasties throughout their lifetime). The clinical expert suggested that an average patient is expected to undergo two arthroplasties during their lifetime. The assumption that patients on prophylaxis do not require any arthroplasties is consistent with the opinion of the clinical expert consulted by CADTH. 7. For quality-of-life impact of arthroplasties, the manufacturer assumed zero utility for one month; however, CADTH reanalysis used a disutility value of –0.39 for one month based on the literature 8. Treatment of AEs: The manufacturer assumed that 30% of treated bleeds would be treated with FEIBA for patients on emicizumab prophylaxis. Concomitant use of emicizumab prophylaxis with an activated prothrombin complex concentrate (such as FEIBA) to treat episodic bleeds is associated with thrombotic microangiopathy and thromboembolism risk when a cumulative amount of > 100 U/kg per 24 hours aPCC was administered for 24 hours or more. According to the clinical expert consulted by CADTH, physicians may therefore choose Niastase over FEIBA to treat bleeds for patients on emicizumab prophylaxis. Treatment with Niastase is associated with higher costs due to increased dose compared with FEIBA; therefore, the assumption that a proportion of the bleeds

								were treated with FEIBA, instead of Niastase, decreased the costs associated with emicizumab treatment. CADTH explored the impact of this assumption in a scenario reanalysis by assuming that 100% of bleeds in patients receiving emicizumab prophylaxis would be treated with Niastase. 9. Costs: Several cost items were not included in the manufacturer's analysis, including physician visit, monitoring for neutralizing antibodies, nurse visits, and central venous access devices placement and the cost of treating infections. While some of these items are relatively low in cost, not including the cost of monitoring of neutralizing antibodies for patients receiving emicizumab and the cost of equipment required to administer emicizumab is likely to underestimate the total cost associated with emicizumab treatment. The cost of emicizumab administration was not available and is likely to vary between centres. Based on feedback from Canadian Blood Services (CBS), an assay to detect neutralizing antibodies is currently being developed and will serve as a Canadian reference. However, the clinical usefulness of an emicizumab-specific anti-drug antibodies assay is uncertain, and the cost associated with monitoring for neutralizing antibodies could not be estimated due to lack of data. Due to lack of information in the manufacturer's submission, the cost of adopting emicizumab as a new technology, including the cost of training professionals to deliver treatment, patient counselling,

								and any additional laboratory testing for monitoring patients was not included in CADTH reanalysis. Hence, the cost estimates should be interpreted with consideration of this limitation. 10. Treatment discontinuation: The manufacturer assumed adherence to be 100% for both emicizumab and BPA prophylaxis, which is unlikely according to CADTH's clinical expert. Previous evidence has shown that adherence to BPA prophylaxis in patients without inhibitors is likely to be between 26% and 96%.21 Higher assumed adherence may overestimate the effectiveness of prophylaxis compared with on-demand treatment. 11. Short follow-up: The economic model, and the predicted costs and benefits of treatments, is based on a lifetime horizon, but the evidence from HAVEN 1 and NIS were conducted over a shorter follow-up period (i.e., the median exposure to emicizumab in the HAVEN 1 clinical trial was 24 weeks; range: 3 to 47.9 weeks). This follow-up was not sufficiently long to make assumptions around the use of emicizumab prophylaxis, or to demonstrate the safety of concomitant use of emicizumab prophylaxis with BPAs to treat bleeding events over a patient's lifetime.
ICER Report								
Health system perspective: Patients ≥ 12 Years of Age:	**Health system perspective: Patients ≥ 12**	**Health system perspective**	**Patients ≥ 12 Years of Age:** Emicizumab	**Patients ≥ 12 Years of Age:** BPA	**Patients ≥ 12 Years of Age:** No		**Patients ≥ 12 Years of Age:** Less costly,	*All input parameters were subjected to sensitivity analyses. The result that emicizumab is cost saving was robust to

Emicizumab Prophylaxis: $19,221,932 **Patients < 12 Years of Age** Emicizumab Prophylaxis: $20,683,787 **Societal perspective:** **Patients ≥ 12 Years of Age:** Emicizumab Prophylaxis: $19,623,275 **Patients < 12 Years of Age** Emicizumab Prophylaxis: $21,212,892	**Years of Age:** BPA Prophylaxis: $90,182,398 No Prophylaxis: $28,135,154 **Patients < 12 Years of Age:** BPA Prophylaxis: $99,212,053 No Prophylaxis: $31,012,935 **Societal perspective:** **Patients ≥ 12 Years of Age:** BPA Prophylaxis: $90,583,742 No Prophylaxis: $28,901,756 **Patients < 12 Years of Age:** BPA Prophylaxis: $99,741,157 No Prophylaxis: $31,695,614	**:** **Patients ≥ 12 Years of Age:** No prophylaxis: - $8,913,222, BPA prophylaxis: - $70,960,466 **Patients < 12 Years of Age:** No prophylaxis: - $10,000,971, BPA prophylaxis: - $78,528,265 **Societal perspective:** **Patients ≥ 12 Years of Age:** No prophylaxis: - $9,278,481, BPA	Prophylaxis: 15.41 **Patients < 12 Years of Age** Emicizumab Prophylaxis: 22.79	Prophylaxis: 15.21 No Prophylaxis: 14.50 **Patients < 12 Years of Age:** BPA Prophylaxis: 22.41 No Prophylaxis: 20.40	prophylaxis: 0.91 BPA prophylaxis: 0.20 (Less Costly, More Effective) **Patients < 12 Years of Age:** No prophylaxis: 2.39 BPA prophylaxis: 0.38 (Less Costly, More Effective)		more effective **Patients < 12 Years of Age:** Less costly, more effective *Emicizumab was estimated to be more effective and to generate more QALYs at lower total cost (cost saving), both from a health system and societal perspective, compared to no prophylaxis and to prophylaxis with BPAs	changes in all input parameters. The incremental QALY gain for emicizumab remained until the utility of "No Bleed" was lowered to a value of 0.66. *Multiple scenario analysis: In all scenarios, emicizumab remained cost saving and had more QALYs gained compared to no prophylaxis and prophylaxis with BPAs.

		prophylaxis: - $70,960,466 (Less Costly, More Effective) **Patients < 12 Years of Age:** No prophylaxis: - $10,482,722, BPA prophylaxis: - $78,528,265 (Less Costly, More Effective)						
Cost -effectiveness studies								
Cost-Effectiveness and Budget Impact of Emicizumab Prophylaxis in Haemophilia A Patients with Inhibitors								
Total costs: €12156904 €171 for emicizumab prophylaxis (cost per patient), €127.30 per mg : public price for	Total costs: aPCC- €32,141,369, rFVIIa- €37,429,094 €521 -aPCC & rFVIIa prophylaxis(cost per patient), €1.22 per IU:	aPCC- 19,984,465 rFVIIa - 25,272,190	Emicizumab:24.49	aPCC-23.55 rFVIIa-23.55	Incremental QALY: 0.94	Willingness-to-pay (WTP) threshold of €100,000 per QALY gained was considered cost-effective, following the threshold	Emicizumab prophylaxis was also the less expensive treatment option with a cost per patient of €12.16 million; while the	PSA was carried out that showed that Emicizumab was cost-saving option. CEAC reported 100% probability of Emicizumab to be cost-effective in all WTP thresholds tested. These results remained robust over a wide range of sensitivity analyses

emicizumab, €77.13 per mg : ex-factory price for emicizumab	public price for aPCC, €1.113 per IU:ex-factory price for Apcc, €0.971 per µg: public price for rFVIIa,€77.13 per mg -ex-factory price for rFVIIa					indicated in the Ollendorf et al study of U.K. and Sweden	rFVIIa prophylaxis was the most expensive one with a cost per patient of €37.43 million. Emicizumab prophylaxis produced a cost saving of €25.2 million and €19.98 million per patient compared with rFVIIa and aPCC prophylaxis, respectively. Based on the higher efficacy and the lower cost, emicizumab prophylaxis was a cost-saving option compared with BPA. Emicizumab prophylaxis increased QALYs and reduced costs compared with BPA	

							prophylaxis, with 0.38 QALY gained and $78.5 million saved compared with BPA prophylaxis. This result confirms our analysis and the cost-saving profile of emicizumab prophylaxis in HA patients with inhibitor.	
Cost-effectiveness of emicizumab vs bypassing agents in the prevention of bleeding episodes in haemophilia A patients with anti-FVIII inhibitors in France								
Reimbursed price: 78.75 €/mg for emicizumab Over five year time horizon: Emicizumab: € 2293969	Reimbursed price: 852.344 €/1000 U for aPCC, and 574.21 €/mg for rFVIIa. Over five year time horizon: BPAs: 2528160 €	Incremental cost: −234191 € (saving per patient)	Emicizumab: 3.22	BPAs: 2.36	Incremental QALY: 0.86		Emicizumab is cost-effecitve when compared to the current treatments using BPAs in France. Emicizuamal also results in significant decrease in health insurance expenditures.	Deterministic sensitivity analysis for incremental costs: Parameters with the highest impact are mainly the drug dosing, the drug distribution for treating the bleeds, the ABR, age distribution and percentage of prophylaxis Deterministic sensitivity analysis for incremental QALY: The two main sources of variation for QALY are the utilities of BPA ondemand and of emicizumab Probabilistic sensitivity analysis: The simulated average decrease in costs and increase in QALYs are close to the results of the base-case analysis, thus confirming the robustness of the results

Cost-utility analysis of emicizumab prophylaxis in haemophilia A patients with factor VIII inhibitors in Korea								
Unit cost per Kg of Emicizumab is 80 USD Emicizumab cost per vial (as suggested by manufacturer): in USD 30 mg (2425) 60 mg (4850) 90 mg (7275) 105 mg (8488) 150 mg (12125) lifetime horizon (>=12 years): total cost (USD): 10 785 885	Drug cost on demand: Drug cost for BPA per bleeding in (/kg) (Expert survey): in USD In emicizumab prophylaxis: 201.4/kg per bleeding episode In BPA on demand treatment: 210.5/kg per bleeding episode total cost (USD): 13 398 772	Cost saving: −2612 886 in a patient's lifetime	Emicizumab: 16.9	BPAs: 13.86	Incremental QALY: 3.04	Per capita GDP of 30,000 USD	Emicizumab prophylaxis represents a cost-saving option that reduces costs while improving clinical outcomes in HAPI as compared to BPA-OD	Both univariate and PSA supprted that emicizumab is a cost saving option

ICER adjustment methods (Detailed version):

a. Simple Adjustment:

To perform a simple adjustment, we multiply the study-reported ICER by the ratio of the price of emicizumab in India (PA) to the price in the original study country (Po), as shown in the following formula. This formula is intended to reflect the fact that in many settings, the price of a new intervention is frequently the main driver of cost-effectiveness findings.

$ICER_A = ICER_O * (P_A / P_O)$

b. Moderate Adjustment:

In cases where the full cost of the intervention in India (i.e the price of treatment and relevant supportive care) is known, it may be possible to extrapolate the cost-effectiveness using data reported in economic evaluations or derived from clinical study findings. The moderate adjustment estimates the monthly treatment cost (Ci) and the mean or median duration of therapy (in months) for both the intervention and its comparator (Mi and Mc, respectively) from the original clinical study or cost-effectiveness analysis (CEA). The formula for the moderate adjustment is as follows:

ICERi = (Ci * Mi) - (Cc * Mc) / ((Mi - Mc) / 12)

Where Ci and Cc represent the monthly cost, and Mi and Mc represent the number of months of treatment for the intervention and comparator, respectively.

c. Complex Adjustment:

In cases where multiple expenses, apart from the intervention cost, may influence the ICER adjustment, or if there are variations in the disease's underlying epidemiology and trajectory between countries, a more sophisticated formula can be employed. This requires separate adjustments for costs and quality-adjusted life years (QALYs), as outlined below:

a. Converted cost = Purchasing power parity (PPP)-adjusted gross domestic product (GDP) per capita, India / PPP-adjusted GDP per capita, study country
b. Inflation factor = Consumer price Index (CPI) for health, India (current year) / CPI for health, India (year of publication)
c. Adjusted cost = (Study-reported cost * a) * b
d. Conversion factor = Life expectancy from diagnosis or birth, India / Life expectancy from diagnosis or birth, study country
e. Adjusted QALYs = Study-reported QALYs * a
f. Adjusted ICER for India = $\Delta Cost_A / \Delta QALY_A$

Evidence summary:

In the final phase of the Rapid Evidence Synthesis (RES) process, after assessing various studies and reports, the pivotal parameters essential for the adjustment methods of Incremental Cost-Effectiveness Ratios (ICERs), encompassing costs and Quality-Adjusted Life Years (QALYs) pertinent to both the intervention and comparator in alignment with this study, were extracted from the comprehensive cost-effectiveness report published by the Institute for Clinical and Economic Review (ICER). Acknowledging ICER's status as an independent and non-partisan research organization, renowned for its stringent and transparent methodologies in review processes, our evidence summary predominantly relies on the critical appraisal articulated in their report. The report itself details the methodology employed for this critical appraisal, ensuring transparency and methodological rigor. (1)

We provide two levels of evidence summaries:

1. Critical appraisal of clinical effectiveness:

We first present a critical appraisal of clinical effectiveness of emicizumab prophylaxis as reported in the ICER report:

There are methodological limitations in the Emicizumab trials, including a relatively short follow-up and the absence of head-to-head randomized comparisons with bypassing agents (BPAs). Despite these limitations, the report highlights the following observations:

- In adults, emicizumab prophylaxis is efficacious in reducing bleeding events compared with no prophylaxis, and it appears more effective than BPAs (aPCC and rFVIIa), based on observational data from the HAVEN 1 trial.
- In children, emicizumab is observed to be more effective in reducing bleeding events than BPAs, although this is based on observational data from the HAVEN 2 trial. Given that BPA prophylaxis itself reduces bleeding events compared with no prophylaxis, the report infers that emicizumab also reduces bleeding events compared with no prophylaxis in children.
- The trials did not measure long-term outcomes, but the report suggests that reducing bleeding events might also reduce joint damage and mortality.

- Safety concerns include thrombotic microangiopathy and thrombotic events, particularly with high doses of aPCC. However, the safety of emicizumab in events altering coagulation or in patients younger than 12 is less certain.
- While not directly reported in trials, emicizumab is considered less burdensome for patients and families than BPAs, given its once-weekly subcutaneous administration compared to multiple weekly intravenous infusions of BPAs.

In summary, for individuals aged 12 and older with hemophilia A and inhibitors, the report expresses high certainty ("A") that emicizumab provides a substantial net health benefit compared with no prophylaxis. For children under 12 and adults, the certainty of a net health benefit is somewhat smaller but still high ("B+"), considering the results of trials and the reduced burden with emicizumab.

Critical Appraisal on the Cost Effectiveness is presented below:

The report's cost-effectiveness analysis indicates that emicizumab prophylaxis is cost-saving compared to no prophylaxis and BPA prophylaxis in hemophilia A patients with inhibitors. Key observations include:

- Emicizumab is estimated to be more effective, generating more QALYs at lower total costs from both a health system and societal perspective compared to no prophylaxis and BPA prophylaxis.
- This conclusion remains robust across a range of sensitivity and scenario analyses, including patient age, bleed rates, adherence, and cost variations.
- Limitations include the absence of long-term data on arthropathy development, reliance on clinical trial data for prophylaxis adherence, and a dependency on short-term outcomes observed in specific clinical trials.
- The economic evaluation's applicability is specific to a defined population: those with hemophilia A and inhibitors who will not undergo or have failed immune tolerance induction (ITI).

In conclusion, the report finds that emicizumab prophylaxis provides gains in quality-adjusted life years at substantially lower costs over a lifetime horizon. The findings are deemed robust across multiple sensitivity and scenario analyses.

References:

1. Institute for Clinical and Economic Review. Emicizumab for Hemophilia A with Inhibitors: Effectiveness and Value [Internet]. United States of America: Institute for Clinical and Economic Review; 2018 Apr [cited 2023 Apr 1] p. 162. Available from: https://icer.org/wp-content/uploads/2020/10/ICER_Hemophilia_Final_Evidence_Report_041618.pdf