Evaluating the cost and intermediary cost-effectiveness of emicizumab prophylaxis in patients with haemophilia A with inhibitors in South Africa

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Affiliation(s) and declaration: LJ and DH (Health Economics and Epidemiology Research Office (HE^{2}RO), University of Witwatersrand) have no interests pertaining to emicizumab.

Introduction

An analysis was conducted to evaluate the cost and budget impact per annum of treating bleeds in patients with haemophilia A with inhibitors, evaluating two arms:

1) patients receiving **emicizumab prophylaxis and their treatment of bleeds using bypassing agents,** and
2) a comparator arm of **on-demand treatment of bleeds only with bypassing agents** (i.e. no prophylaxis)

The analysis considers the payer perspective, taking into account only direct costs to the public health sector. Patient or societal perspective costs were not considered. Long term costs, such as joint replacement costs were also not considered due to the lack of data availability.

Patient population

Initial estimates based on data from the World Federation of Haemophilia, annual global survey and the South Africa Haemophilia Foundation registry data[1] placed the number of patients in public sector with haemophilia A with inhibitors at approximately 160. However, this estimate was based on all patients including those that may bleed infrequently or not at all. Preliminary analysis based on these figures indicated that this may be an overestimate of the number of patients who seek care in the public sector: if assuming 160 patients, then the estimated use of bypassing agents was far higher than current procurement data on bypassing agents, even at modest assumptions on annualised bleed rates (ABR) in this population. Further discussion with experts and feedback from provinces have placed the actual number of people with haemophilia A with inhibitors seeking care in the public sector in a range between 25 and 50. For this reason, we present results using 35 and 160 cases in different scenarios. We also include a scenario which attempts to replicates current procurement cost, which assumes that 55 patients are seeking care for bleeds in the public sector.

We base the age distribution on data of patients at Charlotte Maxeke Hospital in Gauteng, 88% of patients are 19 years or older, 7% are 14-18 years, 5% are 5-13 years, and no patients are <5 years old.[2] No finer age distribution data was available, and therefore the model assumed equal distribution within these age groups. We also ensure that at minimum there is 1 patient per age group (Table 1). Average weight was sourced from the Centers for Disease Control and Prevention (CDC) weight-for-age tables[3] for males (as males tend to be disproportionately affected by haemophilia); adults aged 19+ years were assumed to have an average weight of 70kg.

[1] South African Haemophilia Foundation. Registry data, July 2021
[2] Charlotte Maxeke Academic Hospital Haemophilia data prepared for MASAC submission: 1 July 2021 to 30 June 2022
[3] CDC weight-for-age: https://www.cdc.gov/growthcharts/html_charts/wtage.htm

Table 1. Patient population, estimated number and average weight

Age (years)	Average weight (kg)	Estimated number of patients for N=160	Estimated number of patients for N=55	Estimated number of patients for N=35
5	18.5	1	1	1
6	20.8	1	1	1
7	23.2	1	1	1
8	25.8	1	1	1
9	28.7	1	1	1
10	32.1	1	1	1
11	36.1	1	1	1
12	40.7	1	1	1
13	45.8	1	1	1
14	51.2	2	1	1
15	56.5	2	1	1
16	61.1	2	1	1
17	64.7	2	1	1
18	67.3	2	1	1
19+	70.0	141	41	21
Total		**160**	**55**	**35**

Assumptions around emicizumab prophylaxis

Administration of emicizumab consists of a loading dose (weekly for 4 weeks at 3mg/kg) and thereafter a maintenance dose (either weekly at 1.5mg/kg, 2-weekly at 3mg/kg or 4-weekly at 6mg/kg). Based on discussions with the Tertiary Expert Review Committee (TQ ERC), haemophilia patients (or their parents/guardians) will self-administer emicizumab prophylaxis. During the first two weekly visits in the loading dose phase, a professional nurse will spend time (90 min in week 1 and 45 min in week 2) training patients/parents/guardians on how to self-administer emicizumab. In sensitivity analysis we test the impact of increased training with an additional 45min training by a professional nurse in week 3 and 4 visits.

Assumptions around bleeding episodes and their treatment

The analysis considers only bleeds which require treatment using bypassing agents, including major bleeds and intracranial haemorrhage (ICH). Minor bleeds, which require treatment using tranexamic acid are not considered as often these are treated at home by the patients, treatment is inexpensive, and therefore the costs would be relatively negligible.

Based on discussions with the TQ ERC and clinical experts it was agreed that the ABR sourced from the clinical trials (Oldenburg 2017, 2020) was on the higher side of what is expected in the South African context thus we used the lower bound estimate in some of the scenarios.

The two bypassing agents considered for the treatment of bleeds in patients with haemophilia A with inhibitors is **coagulation factor VIIa recombinant** (product on contract NovoSeven®) and **activated Prothrombin Complex Concentrates** (aPCC) (product on contract FEIBA®). The analysis follows the

current clinical practice treatment guidelines[4] for haemophilia in South Africa, the TQ EML and incorporated expert opinion from specialist doctors in the field.

Bleeding episodes in patients on emicizumab prophylaxis will only be treated with factor Vlla recombinant due to the increased risk of thrombotic events and thrombotic microangiopathies from concomitant use of aPCC[5]. In the comparator arm (i.e. no prophylaxis) we assume that 50% of bleeds will be treated with factor Vlla recombinant, while the remainder with aPCC. Based on expert opinion, sometimes in practice the dosing of bypassing agents is not done as per guidelines due to low availability of stock and there could be some under dosing in patients at first as they assess their clinical progression and increase bypassing agents as needed; the experts advised that this would mostly likely be the case for those on emicizumab given the decreased severity of bleeds due to the prophylaxis. For this reason, in some scenarios we assume half the dose of factor Vlla recombinant in the most common treatment strategy for patients on emicizumab, i.e. assuming 45µg/kg instead of instead of 90µg/kg 2-3hourly. We do vary this across out different scenarios. We also make assumptions regarding the proportion of bleeds that are treated in the public sector and assume both 30% and 100% in different scenarios; this was to get as close to possible to recreating the current expenditure on bypassing agents in the public sector based on procurement data.

We assumed no vial sharing, and surgery and other complications of bleeding episodes were not considered.

Scenarios and sensitivity analysis

We model four scenarios (Scenarios 1-4), their key differences in assumptions depicted in Table 2.

Table 2. Key differences in assumptions between four scenarios modelled

<table>
<tr><th></th><th>Scenario 1</th><th>Scenario 2</th><th>Scenario 3</th><th>Scenario 4</th></tr>
<tr><td>Number of cases</td><td colspan="2">N=35</td><td>N=55</td><td>N=160</td></tr>
<tr><td>Annual bleed rate (ABR)</td><td colspan="3">13.2 (children); 12.3 (adults)
Lower bound estimates from Oldenburg (2020), Oldenburg (2017)</td><td>19.4 (children);
23.3 (adults)
Mid-point estimates from Oldenburg (2020), Oldenburg (2017)</td></tr>
<tr><td>% of bleeds treated in public sector</td><td colspan="2">100%</td><td colspan="2">30%</td></tr>
<tr><td>Hospital length of stay for treating bleeds between arms</td><td>Differential.
<u>Emicizumab</u>:
4 days in hospital
<u>Comparator</u>:
9 days in hospital</td><td colspan="3">Same.
Both arms: 9 days in hospital</td></tr>
<tr><td>Dosing of bypassing agents for bleeds between arms</td><td>Differential.
<u>Emicizumab</u>:
half dose of factorVIIa (45µg/kg)
<u>Comparator</u>:
full dose of factorVIIa (90µg/kg)</td><td colspan="2">Same.
Both arms: half dose of factorVIIa (45µg/kg)</td><td>Same.
Both arms: full dose of factorVIIa (90µg/kg)</td></tr>
</table>

To note is that **Scenario 3 gets close to replicating the current procurement cost of bypassing agents** in the comparator arm, and was created for comparison purposes. The current estimated annual cost

[4] Mahlangu, Gilham (2008). Medical and Scientific Advisory Council of the South African Haemophilia Foundation. Guideline for the treatment of haemophilia in South Africa.

[5] Oldenburg et al (*NEJM*, 2017). Emicizumab Prophylaxis in Hemophilia A with Inhibitors.

of procuring bypassing agents in the public sector is approximately R85.6 million (standard deviation: R69.9 million to R97.7 million), the average across 2020-2022[6].

More details on assumptions regarding number of bleeds per arm, time of treatment, hospitalization are in *Figure 3. Average patient cost* **per year by annual bleed rate (ABR) and scenario**

The average cost per patient year is lower in the emicizumab arm for ABR of 4 bleeds per annum (Scenario 1), 6 bleeds per annum (Scenario 2), 16 bleeds per annum (Scenario 3) and 12 bleeds per annum (Scenario 4) (Figure 3). **Across all scenarios the average cost per patient year ranges between R1.6-R2.5 million and remains relatively stable over all ABRs**, whereas the average cost per patient year varies substantially between scenarios and ABR for the comparator arm.

Summary

There is considerable uncertainty regarding the data used to parameterize the model, including current number of patients with haemophilia A with inhibitors who seek care in the public sector, the annual number of bleeds that experienced, treated with bypassing agents, and the extent to which patients in public sector are potentially under-dosed with bypassing agents once they seek care. This uncertainty was evident as the model was unable to align potential patient need to current expenditure on bypassing agents, unless it involved making several assumptions around patient numbers, care-seeking and dosing.

To address the uncertainty, this analysis looked at different scenarios. Each scenario had a different threshold for ABRs where emicizumab may be cost-saving. Three out of the four scenarios showed the emicizumab arm to be cost saving (scenario 1, 2, and 4) with scenario 3 (attempt to match procurement data) favouring the standard of care arm. In sensitivity analysis the emicizumab arm became cost-saving with an ABR of 16. However, across all scenarios the average per patient cost of those in the emicizumab arm had a relatively narrow range of R1.6-R2.5 million per year, despite the different ABR estimates assumed (though dependent on the assumed 87% effectiveness from trial data). This means that if spending more than R2-R2.5 million per person on average per year on bypassing agents, emicizumab is likely a cost-saving intervention.

Another limitation was the lack of data on long-term outcomes, and as a result we did not incorporate the impact and cost of other complications, surgeries, disability or quality of life.

It is important to highlight other literature which evaluated the cost-effectiveness of emicizumab compared to on-demand treatment of bleeds. A rapid review (conducted in May 2023) of the literature on economic evaluations of emicizumab found 6 studies[,,,,]. These were conducted in Malaysia, South Korea, Iran, France, Italy, and United States. Of the 6 studies, 5 found emicizumab to be dominant and cost-saving at ABRs ranging between 7.9 and 46.6 bleeds per annum. Further, Samelson-Jones et al (2020) who conducted a real-world cost analysis found that emicizumab was cost-saving largely because of a decrease in the total cost of high-cost outliers16.

[6] Public Sector Depot Procurement data – Retrieved October 2023, Deliveries for January 2020 to December 2022.

Supplementary Table 1: Model assumptions.

We further conducted a deterministic way sensitivity analysis to explore the impact of key parameters on the cost per bleed averted.

Costs

Costs for factor Vlla recombinant and aPCC were sourced from the National Department of Health Master Health Product List[7] (contract prices). Costs for emicizumab prophylaxis were sourced from the current state sector offer price[8]. Sensitivity analysis included prices from the South African Medicines Price Registry's single exit price (SEP)[9], including assuming a 60% of SEP.

Staff costs for the administration and training of self-administration of emicizumab prophylaxis was sourced from the Department of Public Service and Administration (DPSA) government salary scales (April 2023)[10]. Facility fees for outpatient (for initial emicizumab provision), facility fees for inpatient (for treatment of bleeding episodes), and staff costs for hospitalization were sourced from the Uniform Patient Fee Schedule[11] (dated April 2023); consumables were assumed to be included in the facility fees.

Results

In Scenarios 1,2 and 4, treating patients with haemophilia A with inhibitors is cost-savings ranging between saving R94.4 million to R352 million per year, depending on the number of cases, ABR and treatment of bleeds strategy (Table 3). **In Scenario 3**, which replicates current cost of procurement of bypassing agents in the comparator arm, the incremental cost per bleed averted is estimated at R84,594.

[7] South African National Department of Health. Master Health Product List – Version May 2023
[8] Roche – State sector offer price for Hemlibra - 2023
[9] National Department of Health. South African Medicines Price Registry. Available at: https://medicineprices.org.za/ - Accessed July 2023
[10] Department of Public Service and Administration (DPSA) government salary scales, 1 April 2023. Available at: https://www.dpsa.gov.za/dpsa2g/documents/rp/2023/Appendices%20A%20to%20H%20to%20Circular%2020%20of%202023%20(COLA).xlsx Accessed August 2023
[11] National Department of Health. Uniform Patient Fee Schedule Procedure Book. Annexure A2 UPFS tariffs - 1 April 2023 - FULL PAYING. Available at: https://www.health.gov.za/uniform-patient-fee-schedule/ - Accessed August 2023

Table 3. One year cost and impact on bleeds, by scenario

	Scenario 1	Scenario 2	Scenario 3	Scenario 4
Short description *(see Table 2 for detail)*	N=35, ABR lower bound, 100% bleeds treated, hospital length of stay shorter in emicizumab arm, bypassing agents dosing half in emicizumab arm	N=35, ABR lower bound, 100% bleeds treated, hospital length of stay same as comparator arm, bypassing agents half dose across arms	N=55, ABR lower bound, 30% bleeds treated, hospital length of stay same as comparator arm, bypassing agents half dose across arms	N=160, ABR midpoint, 30% bleeds treated, hospital length of stay same as comparator arm, bypassing agents full dose across arms
Costs (ZAR)				
Emicizumab prophylaxis	R54,211,136	R54,211,136	R89,195,303	R272,344,816
Emicizumab treatment of bleeds	R19,327,746	R19,797,128	R9,940,568	R90,017,551
Emicizumab prophylaxis + treatment of bleeds	**R73,538,882**	**R74,008,264**	**R99,135,871**	**R362,362,367**
Comparator treatment of bleeds	**R246,886,169**	**R168,405,976**	**R84,179,262**	**R714,508,227**
Incremental cost of emicizumab arm	*-R173,347,287*	*-R94,397,712*	*R14,956,610*	*-R352,145,860*
Number of bleeds treated				
Emicizumab arm	60	60	28	138
Comparator arm	437	437	205	1,111
Bleeds averted	377	377	177	973
Incremental cost per bleed averted	**-R459,792 (cost-saving)**	**-R250,383 (cost-saving)**	**R84,594**	**-R361,981 (cost-saving)**

Achieving price neutrality in Scenario 3

The price of emicizumab needs to decrease by 17% compared to the state sector price offer in order to be cost-neutral, under our assumptions made in Scenario 3 (which replicates current cost of procurement of bypassing agents in the comparator arm).

Table 4: Cost-neutral price estimate for emicizumab

Emicizumab price per vial	State sector price offer	Cost-neutral price estimate
Hemlibra 30mg/1MI	R8,920	R7,423
Hemlibra 60mg/0.4MI	R17,840	R14,847
Hemlibra 105mg/0.7MI	R31,220	R25,982
Hemlibra 150mg/1MI	R44,601	R37,117

Sensitivity analysis

In deterministic sensitivity analysis we varied several parameters: ABR, emicizumab effectiveness, emicizumab drug price, cost of provision of emicizumab (i.e. service cost, staff only), cost of hospital stay in general ward and intensive care.

For Scenarios 1 and 2, where we assume that 100% of bleeds are treated in the public sector, emicizumab remained dominant across all changes of parameters. For Scenarios 3 and 4, where we assume that only 30% of bleeds are treated in public sector, cost per bleed averted differed with a change in ABR, emicizumab effectiveness and the cost of emicizumab (Figures 1.1-1.4). Across all scenarios, the cost of hospitalisation and service provision of emicizumab had little impact on cost per bleed averted.

As annual bleed rate made a substantial impact on the cost per bleed averted, we also plot the cost per bleed averted for varying ABR (Figure 2) as well as the estimated average per patient cost per arm

(treatment of bleeds + prophylaxis, if applicable) by varying ABR (Figure 3). This can help assess whether there may be an ABR criteria where emicizumab becomes dominant.

Figure 1.1. Scenario 1: tornado diagram for deterministic sensitivity analysis *(short description: N=35, ABR lower bound, 100% bleeds treated, hospital length of stay shorter in emicizumab arm, bypassing agents dosing half in emicizumab arm)*

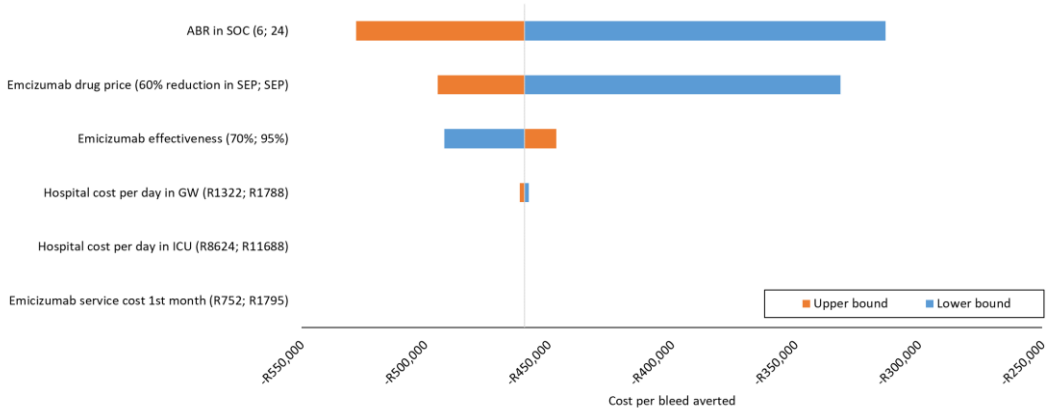


Figure 1.2. Scenario 2: tornado diagram for deterministic sensitivity analysis *(short description: N=35, ABR lower bound, 100% bleeds treated, hospital length of stay same as comparator arm, bypassing agents half dose across arms)*

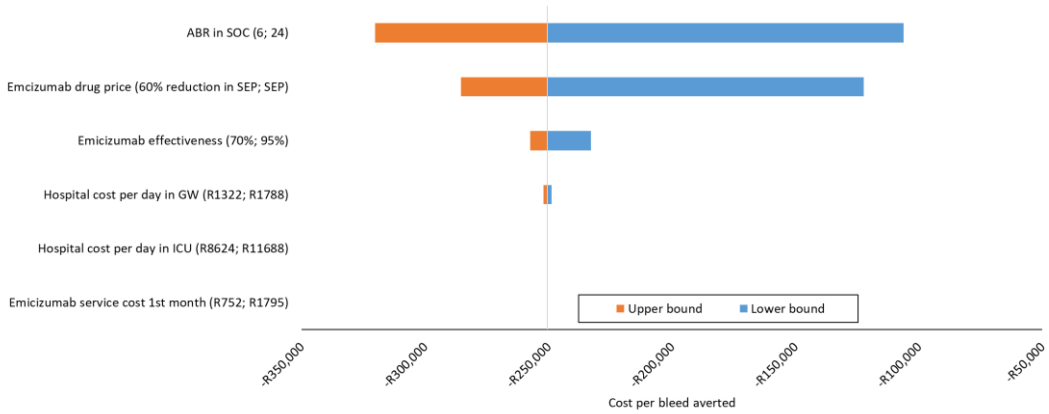


Figure 1.3. Scenario 3: tornado diagram for deterministic sensitivity analysis *(short description: N=55, ABR lower bound, 30% bleeds treated, hospital length of stay same as comparator arm, bypassing agents half dose across arms)*

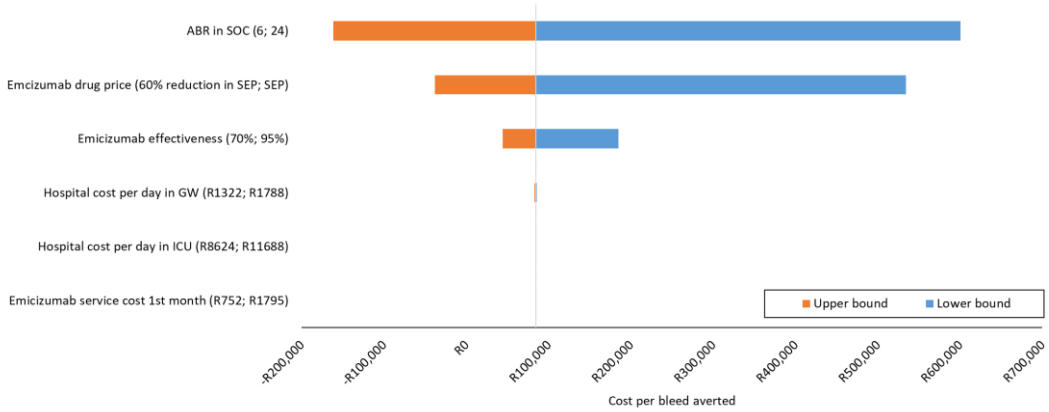


Figure 1.4. Scenario 4: tornado diagram for deterministic sensitivity analysis *(short description: N=160, ABR midpoint, 30% bleeds treated, hospital length of stay same as comparator arm, bypassing agents full dose across arms)*

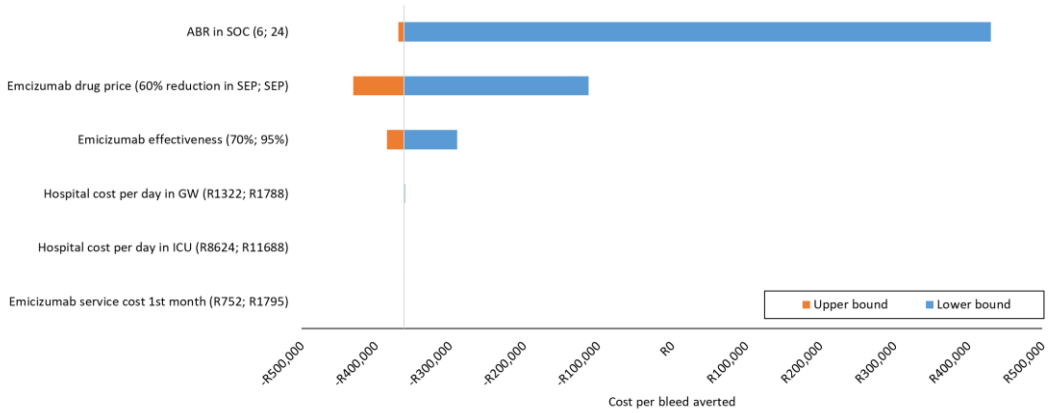
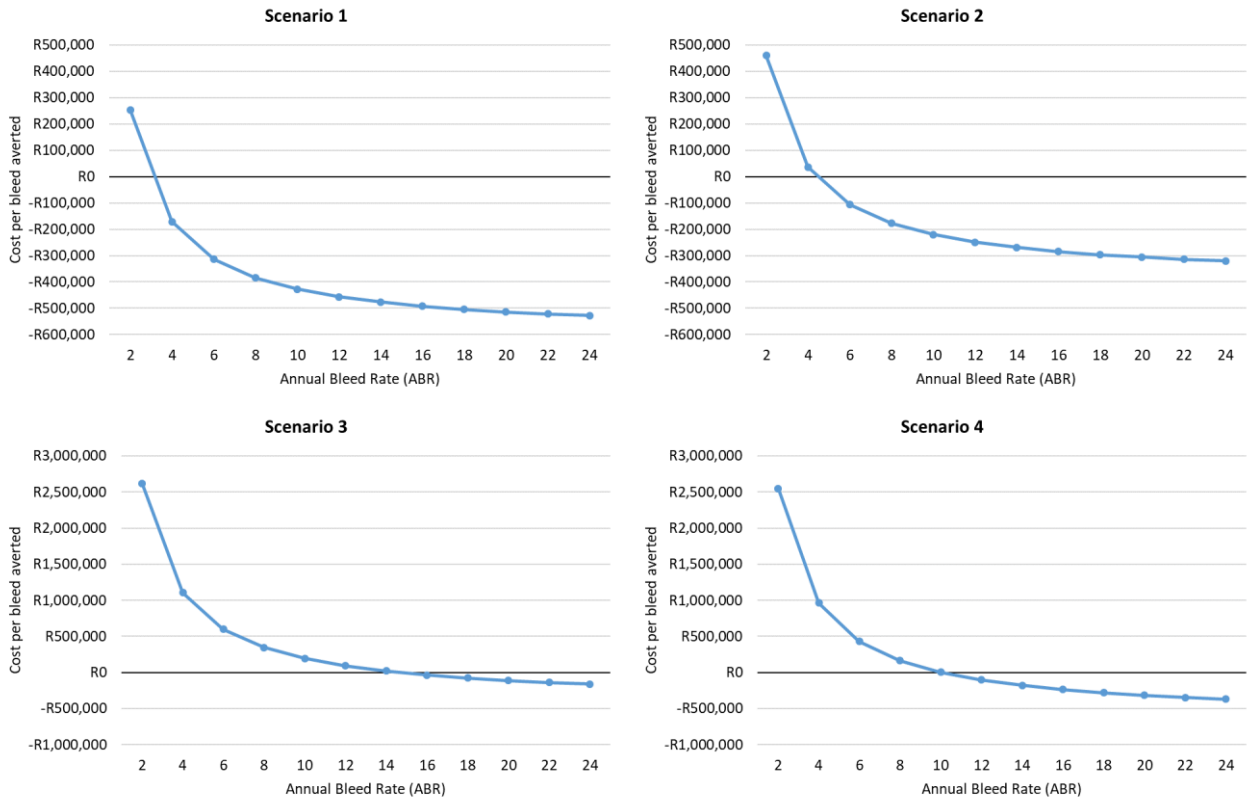


Figure 2. Cost per bleed averted by annual bleed rate (ABR) and scenario



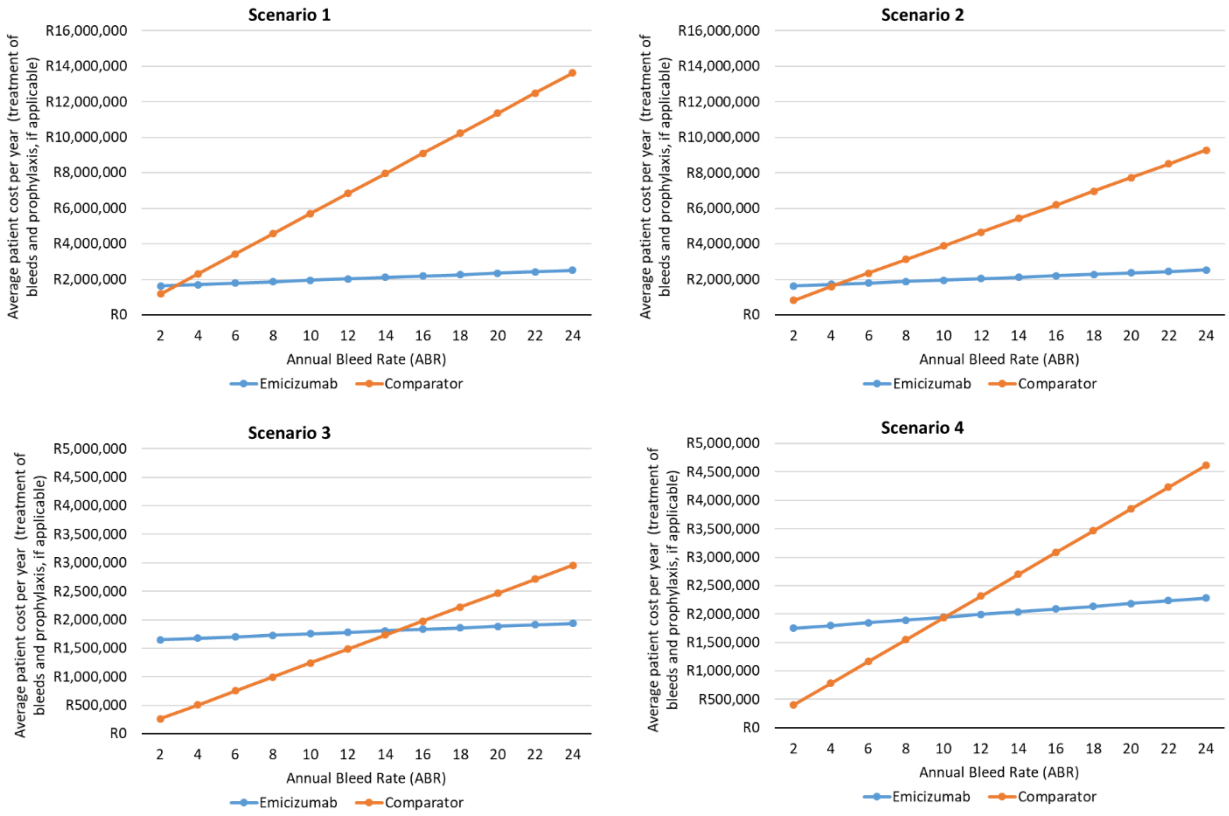
In Scenario 1, where we assume N=35 cases, ABR lower bound, 100% of bleeds were treated, hospital length of stay shorter in emicizumab arm, bypassing agents dosing half in emicizumab arm, **emicizumab remained cost-savings compared to the comparator arm for ABRs of 4 bleeds/annum or higher** (Figure 2)**.**

In Scenario 2, where we assume N=35 cases, ABR lower bound, 100% of bleeds were treated, hospital length of stay was the same in the emicizumab arm as the comparator arm, bypassing agents half dose across arms, **emicizumab became cost-saving for ABR of 6 bleeds/annum or higher** (Figure 2).

In Scenario 3, where we assume N=55 cases, ABR lower bound, 30% of bleeds were treated, hospital length of stay was the same in the emicizumab arm as the comparator arm, bypassing agents half dose across arms- a*nd the scenario which replicates the current cost of procurement of bypassing agents* - **emicizumab became cost-saving for ABR of 16 bleeds/annum or higher** (Figure 2).

In Scenario 4, where we assume N=160 cases, ABR midpoint, 30% of bleeds were treated, hospital length of stay was the same in the emicizumab arm as the comparator arm, bypassing agents full dose across arms, **emicizumab became cost-saving for ABR of 12 bleeds/annum or higher** (Figure 2).

Figure 3. Average patient cost per year by annual bleed rate (ABR) and scenario



The average cost per patient year is lower in the emicizumab arm for ABR of 4 bleeds per annum (Scenario 1), 6 bleeds per annum (Scenario 2), 16 bleeds per annum (Scenario 3) and 12 bleeds per annum (Scenario 4) (Figure 3). **Across all scenarios the average cost per patient year ranges between R1.6-R2.5 million and remains relatively stable over all ABRs**, whereas the average cost per patient year varies substantially between scenarios and ABR for the comparator arm.

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To address the uncertainty, this analysis looked at different scenarios. Each scenario had a different threshold for ABRs where emicizumab may be cost-saving. Three out of the four scenarios showed the emicizumab arm to be cost saving (scenario 1, 2, and 4) with scenario 3 (attempt to match procurement data) favouring the standard of care arm. In sensitivity analysis the emicizumab arm became cost-saving with an ABR of 16. However, across all scenarios the average per patient cost of those in the emicizumab arm had a relatively narrow range of R1.6-R2.5 million per year, despite the different ABR estimates assumed (though dependent on the assumed 87% effectiveness from trial

data[12]). This means that if spending more than R2-R2.5 million per person on average per year on bypassing agents, emicizumab is likely a cost-saving intervention.

Another limitation was the lack of data on long-term outcomes, and as a result we did not incorporate the impact and cost of other complications, surgeries, disability or quality of life.

It is important to highlight other literature which evaluated the cost-effectiveness of emicizumab compared to on-demand treatment of bleeds. A rapid review (conducted in May 2023) of the literature on economic evaluations of emicizumab found 6 studies[13,14,15,16,17,18]. These were conducted in Malaysia, South Korea, Iran, France, Italy, and United States. Of the 6 studies, 5 found emicizumab to be dominant and cost-saving at ABRs ranging between 7.9 and 46.6 bleeds per annum. Further, Samelson-Jones et al (2020) who conducted a real-world cost analysis found that emicizumab was cost-saving largely because of a decrease in the total cost of high-cost outliers[16].

[12] Oldenburg et al (*NEJM*, 2017). Emicizumab Prophylaxis in Hemophilia A with Inhibitors.
[13] Watanabe et al (*Value in Health*, 2022). Budget Impact of Emicizumab for Routine Prophylaxis of Bleeding Episodes in Patients With Hemophilia A With Inhibitors.
[14] Lee et al (*Haemophilia*, 2020). Cost-utility analysis of emicizumab prophylaxis in haemophilia A patients with factor VIII inhibitors in Korea.
[15] Polack et al (*Haemophilia*, 2021). Cost-effectiveness of emicizumab vs bypassing agents in the prevention of bleeding episodes in haemophilia A patients with anti-FVIII inhibitors in France.
[16] Samelson-Jones et al (*Haemophilia*, 2021). Real-world cost estimates of initiating emicizumab in US patients with haemophilia A.
[17] Cortesi et al (*Thrombosis and Haemostasis,* 2019). Cost-Effectiveness and Budget Impact of Emicizumab Prophylaxis in Haemophilia A Patients with Inhibitors.
[18] Saiyarsarai et al (*Medicine*, 2021). A comparison between on-demand usage of rFVIIa vs prophylaxis use of emicizumab in high titer inhibitory hemophilia A patients in Iran.

Supplementary Table 1: Model assumptions

Parameter	Value *(The same across scenarios unless stated otherwise)*	Range for sensitivity analysis, if applicable	Source
No. of patients in public sector	35 (Scenarios 1-2) 55 (Scenario 3); 160 (Scenario 4)	-	World Federation of Haemophilia, annual global survey; South Africa Haemophilia Foundation registry data[19]; expert opinion
Outcomes, treatment of bleeds			
Annual Bleed Rate (ABR): major bleeds requiring bypassing agents			
Not on emicizumab prophylaxis			
children<12 yrs	13.2 (Scenarios 1-3) 19.4 (Scenario 4)	2-24	Oldenburg (2020)[20]
adults 12+	12.3 (Scenarios 1-3) 23.3 (Scenario 4)	2-24	Oldenburg (2017)[21]
On emicizumab prophylaxis			
children<12 yrs	1.8 (Scenarios 1-3) 2.4 (Scenario 4)	Apply 87% effectiveness estimate to comparator arm	Assume same efficacy as for adults
adults 12+	1.7 (Scenarios 1-3) 2.9 (Scenario 4)		Oldenburg (2017)[21]
Incidence of intracranial haemorrhage (ICH), per year			
Not on emicizumab prophylaxis			
All patients	0.017	-	Andersson (2017)[22]
On emicizumab prophylaxis			
All patients	0.00033	-	Andersson (2017)[22]
Treatment of bleeds			
Major bleeds requiring bypassing agents			
% of bleeds treated in public sector	100% (Scenarios 1-2) 30% (Scenarios 3-4)	-	Assumption
FactorVIIa – not on emicizumab			
Treatment strategy			
% 90µg/kg 2-3hourly	50%	-	Expert opinion (Tertiary ERC)
% 20µg/kg/hr infusion	40%	-	
% single dose 270µg/kg	10%	-	
Dose reduction in 2-3 hourly strategy	0%	-	Expert opinion (Tertiary ERC)
No. of days of treatment	1	-	Expert opinion (Tertiary ERC)
No. of days hospitalized	9	-	Polack (2021)[23]
% treated with FactorVIIa vs aPCC in comparator arm	50%	-	Assumption
FactorVIIa – on emicizumab			
Treatment strategy			
% 90µg/kg 2-3hourly	100%	-	Expert opinion (Tertiary ERC)
% 20µg/kg/hr infusion	0%	-	
% single dose 270µg/kg	0%	-	
Dose reduction in 2-3 hourly strategy	50% (Scenario 1); 0% (Scenarios 2-4)	-	Expert opinion (Tertiary ERC)
No. of days of treatment	1	-	Expert opinion (Tertiary ERC)
No. of days hospitalized	4 (Scenario 1); 9 (Scenarios 2-4)	-	Polack (2021)[23]
aPCC – not on emicizumab			

[19] South African Haemophilia Foundation. Registry data, July 2021

[20] Oldenburg et al (*Pediatr Blood Cancer*, 2020). Outcomes in children with hemophilia A with inhibitors: Results from a noninterventional study.

[21] Oldenburg et al (*NEJM*, 2017). Emicizumab Prophylaxis in Hemophilia A with Inhibitors.

[22] Andersson et al (*Br J Haematol*, 2017). Intracranial haemorrhage in children and adolescents with severe haemophilia A or B - the impact of prophylactic treatment.

[23] Polack et al (*Haemophilia*, 2021). Cost-effectiveness of emicizumab vs bypassing agents in the prevention of bleeding episodes in haemophilia A patients with anti-FVIII inhibitors in France.

Parameter	Value *(The same across scenarios unless stated otherwise)*	Range for sensitivity analysis, if applicable	Source
No. of days of treatment	5	-	Expert opinion (Tertiary ERC)
No. of days hospitalized	5	-	Expert opinion (Tertiary ERC)
Dose reduction	0%	-	Expert opinion (Tertiary ERC)
Intracranial Haemorrhage (ICH)			
% of hospital time spent in ICU	50%	-	Expert opinion (Tertiary ERC)
FactorVIIa for ICH			
Treatment strategy			
% 90µg/kg 2-3hourly	80%	-	Expert opinion (Tertiary ERC)
% 20µg/kg/hr infusion	10%	-	
% single dose 270µg/kg	10%	-	
No. of days of treatment	10	-	Expert opinion (Tertiary ERC)
No. of days hospitalized	10	-	Expert opinion (Tertiary ERC)
% treated with FactorVIIa vs aPCC in comparator arm	100%	-	Assumption
aPCC for ICH			
No. of days of treatment	10	-	Expert opinion (Tertiary ERC)
No. of days hospitalized	10	-	Expert opinion (Tertiary ERC)
Costs			
Drug costs: emicizumab (state sector prices for main analyses)			
30mg vial	R8,920	R6,748-R18,069	Roche – State sector offer price for Hemlibra (2023)[24]; ranges informed by 60% reduction in SEP and SEP from Medicine Price Registry (2023)[25]
60mg vial	R17,840	R13,497-R35,911	
105mg vial	R31,220	R23,620-R62,672	
150mg vial	R44,601	R33,742-R89,433	
Drug costs: FactorVIIa			
1mg vial	R8,776	-	Master Health Product List (2023)[26]
2mg vial	R17,552	-	
5mg vial	R43,879	-	
Drug costs: aPCC			
500IU vial	R9,314	-	Master Health Product List (2023)[26]
1000IU vial	R18,629	-	
Cost of emicizumab provision i. Professional nurse for loading dose visits, training for self-administration (90min in week 1, 45min in week 2 visits) ii. Outpatient facility fee	R884	R752-R1,795	DPSA government salary scales (April 2023)[27], Uniform Patient Fee Schedule (2023)[28]
Hospitalisation cost/day (general ward) i. General medical practitioner ii. Nursing medical practitioner Inpatient facility fee (level 2)	R1,555	R1,322-R1,788	Uniform Patient Fee Schedule (2023) [28]
Hospitalisation cost/day (ICU) i. General medical practitioner ii. Nursing medical practitioner Inpatient facility fee (level 2)	R10,146	R8,624-R11,668	Uniform Patient Fee Schedule (2023) [28]

[24] Roche. State sector offer price for Hemlibra - 2023
[25] National Department of Health. South African Medicines Price Registry. Available at: https://medicineprices.org.za/ - Accessed July 2023
[26] South African National Department of Health. Master Health Product List – Version May 2023
[27] Department of Public Service and Administration (DPSA) government salary scales, 1 April 2023. Available at: https://www.dpsa.gov.za/dpsa2g/documents/rp/2023/Appendices%20A%20to%20H%20to%20Circular%2020%20of%202023%20(COLA).xlsx Accessed August 2023
[28] National Department of Health. Uniform Patient Fee Schedule Procedure Book. Annexure A2 UPFS tariffs - 1 April 2023 - FULL PAYING. Available at: https://www.health.gov.za/uniform-patient-fee-schedule/ - accessed August 2023