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Cost-minimization and budget impact analysis of bypassing agents in hemophilia A with inhibitors: a Brazilian study

Análise de custo-minimização e impacto orçamentário de agentes de bypass na hemofilia A com inibidores: um estudo brasileiro

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ABSTRACT

Objective: The aim of the study was to compare the treatment with plasma-derived activated prothrombin complex concentrate (APCC) and recombinant activated FVII (rFVIIa) in patients with Hemophilia A with inhibitors, analyzing the costs and budget impact of prophylactic and on-demand treatment in the Brazilian Unified Health System (In Portuguese, *Sistema Único de Saúde* [SUS]). **Methods**: This study performs a Cost-Minimization Analysis (CMA) and a Budget Impact Model (BIM) for APCC versus rFVIIa in the prophylaxis and on-demand treatment in SUS perspective, based on analysis of guidelines and public databases from Brazil. **Results:** The cost per patient for prophylaxis is estimated to be lower with APCC than in rFVIIa for the maximum dose with an incremental cost difference of BRL 2,730,798 (APCC BRL 3,325,894 versus rFVIIa BRL 6,056,692). The BIM estimated that 5 years after the partial substitution of rFVIIa for APCC (30% and 70%, respectively) brings the potential saving of BRL 201,622,888 considering prophylaxis in adults and BRL 83,095,850 in children. For on-demand usage, the amount saved could be BRL 42,696,097 in adults and BRL 17,596,556 in children. **Conclusion:** This analysis suggests a potential cost saving from payer's perspective (SUS) using APCC instead rFVIIa for Hemophilia A patients with inhibitors, mainly for prophylaxis. The results could potentially bring value to patients and payers as resources could be reallocated to provide more care with the same budget, considering patient clinic response.

Keywords: Blood Coagulation Factors; Hemophilia A; Blood Coagulation Factor Inhibitors; Hematologic Agents; Factor VIIa; Health Care Economics and Organizations

RESUMO

Objetivo: O objetivo do estudo foi comparar o tratamento com concentrado de complexo protrombínico ativado derivado do plasma (APCC) e FVII ativado recombinante (rFVIIa) em pacientes com hemofilia A com inibidores, analisando os custos e o impacto orçamentário do tratamento profilático e sob demanda no Sistema Único de Saúde (SUS). **Métodos:** Este estudo realiza uma Análise de Custo-Minimização (CMA) e um Modelo de Impacto Orçamentário (MIO) para APCC versus rFVIIa na profilaxia e tratamento sob demanda na perspectiva do SUS, com base na análise de diretrizes e bancos de dados públicos do Brasil. **Resultados:** Estima-se que o custo por paciente para profilaxia seja menor com APCC do que com rFVIIa para a dose máxima, com uma diferença de custo incremental de R$ 2.730.798 (APCC R$ 3.325.894 versus rFVIIa R$ 6.056.692). O MIO estimou que, cinco anos após a substituição parcial de rFVIIa por APCC (30% e 70%, respectivamente), a economia potencial seria de R$ 201.622.888 considerando a profilaxia em adultos e R$ 83.095.850 em crianças. Para o uso sob demanda, o valor economizado poderia ser de R$ 42.696.097 em adultos e R$ 17.596.556 em crianças. **Conclusão:** Essa análise sugere uma potencial economia de custos do ponto de vista do pagador (SUS) usando APCC em vez de rFVIIa para pacientes com hemofilia A com inibidores, principalmente para profilaxia. Os resultados poderiam potencialmente trazer valor para pacientes e pagadores, pois os recursos poderiam ser realocados para fornecer mais cuidados com o mesmo orçamento, considerando a resposta clínica do paciente.

Palavras-chave: Fatores de Coagulação Sanguínea; Hemofilia A; Inibidores do Fator de Coagulação Sanguínea; Agentes Hematológicos; Fator VIIa; Economia e Organizações de Saúde

Introduction

Hemophilia A is an inherited coagulopathy characterized by plasma deficiency of coagulation factor VIII, which generates high risk for bleeding, mainly inside the joints and muscle, as well as prolonged bleeding following trauma or surgery.[1] The disease is classified according to the residual clotting activity of the factor VIII into mild, moderate and severe[2] and, according to the World Federation of Hemophilia – WFH 2022 data, about 34% of the patients with hemophilia have severe form of the disease.[3] The prevention or treatment of bleeding events require the intravenous infusion of the deficient clotting factor, either of plasmatic or recombinant origin. Recently, new molecules which have the goal on thrombin generation are also emerging as a therapeutic approach. Non-replacement treatment is becoming an alternative to prevent bleeding in these patients.

A complication due to the treatment that might occur with hemophilia patients is the development of inhibitors. Inhibitors are alloantibodies (antibodies of the IgG class) developed in response to FVIII replacement, that typically neutralize the function of infused clotting factor concentrates.[4] This condition reduces the efficacy of hemostatic treatment and clearly causes significantly worsened morbidity[5,6], providing a life expectancy disadvantage/decrease, which for high-income countries is 37% for severe hemophilia A.[7]

Patients with inhibitors commonly present a severe manifestation of the disease. According to recent estimates from established national patient registries, also cited in the World Federation of Hemophilia (WFH) 2022 report[3], the prevalence for hemophilia A for both severe and all patients is, approximately, 9.5 per 100,000 males and 6.0 per 100,000 males, respectively. The difference in these epidemiological parameters shows how the burden of the disease could mean loss years of life.[7]

Studies suggest a cumulative risk of inhibitors ranging from 20% to 30% of hemophilia A patients.[4] Inhibitors develop less frequently in mild/moderate than in severe hemophilia A; however, all patients with hemophilia are potentially at risk.[5]

In cases of severe hemophilia A with inhibitors, it is necessary to explore other treatment options, as factor VIII therapy cannot respond adequately and can lead to an increase in the frequency and/or severity of bleeding episodes. In these cases, infusion of bypassing agents is suggested as alternative therapy to treat or prevent bleeding episodes.[8]

The Brazilian Universal Public Healthcare System (In Portuguese, "Sistema Único de Saúde [SUS]) has a strong hemophilia public healthcare policy to assist hemophilic patients in all their care journey. The Hemophilia Manual of the Ministry of Health (2015) and the Diagnosis and Treatment Manual for Inhibitors in Patients with Congenital Hemophilia (2022) recommend that all patients with inhibitors for factor VIII undergo induction of immunotolerance, intermittent prophylaxis (or short-term prophylaxis) with the aim of preventing bleeding or interrupting/alleviating hemorrhagic complications.[9,10] Immunotolerance aims to induce tolerance and cease the production of anti-factor VIII antibodies through regular, frequent, and prolonged exposure to high doses of the deficient coagulation factor against which the patient developed an inhibitor (in this case, FVIII) and through the association of a bypass agent to allow hemostatic control in patients with inhibitors.[11]

Recombinant activated FVII (rFVIIa) and plasma-derived activated prothrombin complex concentrate (APCC) are the bypassing agents available at the Brazilian Universal Public Healthcare System for controlling/preventing bleedings.[9,10,12] They can activate the coagulation cascade and maintain hemostasis by triggering thrombin generation[13], as well as preventing joint and soft tissue hemorrhage and reducing joint damage and disability when used as prophylactic treatment.[14,15] The efficacy and safety of bypassing agents to prevent and control bleeding episodes in hemophilia patients with inhibitors have been widely documented in the literature.[12,14-16]

An important point to consider is the clinical response of the patient, that sometimes could become refractory to one product treatment, resulting in a condition that would consume more product without adequate bleeding control. Then treatment choice may consider even the clinical response and the economic burden.

Hemophilia treatment represents a significant financial burden for the health care system, with

clotting factor costs accounting for 45%-93% of the total health care costs, depending on severity and the treatment regimen.[17,18] For hemophilia patients with inhibitors, these numbers are significantly higher due to the bypassing agents' costs, mainly in the prophylaxis regimen, when the replacement improves relevantly the quality of life.[17-19]

In this scenario, having a valid estimate of economic impact among the products used in hemophilia A specific population, would improve the health care system efficiency. Especially in Brazil, which represents the fourth biggest population with hemophilia patients in the world, thus the budget for public health care system is significant. The purpose of this study was to: i) assess and compare the costs of APCC and rFVIIa treatment when used in hemophilia A patients with inhibitors in a cost minimization analysis and ii) compare the budget impact with both treatments in the Brazilian Public Health System (SUS).

Methods

Cost minimization analysis - CMA

A CMA model was developed to evaluate the use of bypassing agents when preventing or treating bleedings (in cases that on-demand treatment is necessary) in people with hemophilia A with inhibitors. The objective of this analysis was to estimate the potential reduction in costs with the use of one drug instead of another (APCC versus rFVIIa) considering similar clinical situations for treatment of active bleeding (on demand) and prevention of bleeding (prophylactic).

In such model, only costs are compared because the efficacy and the safety of both drugs was considered similar, according to a Cochrane systematic review.[12] The CMA model included direct costs (administration and treatment itself, which could be either prophylactic or on-demand) and adopted the SUS perspective. A period of 1 year was assumed as a time horizon for this analysis. All costs are expressed in reais (BRL), and the model was developed using the Microsoft Excel®. The analysis provided the difference in the per-patient costs of prophylactic and on demand treatment.

Model Inputs

The doses regimens are based on the Manual of Diagnosis and Treatment of Inhibitor in Patients with Congenital Hemophilia[11] and on the Protocol for the Use of Immunotolerance Induction for Individuals with Hemophilia A and Inhibitor[8], both published by the Brazilian Ministry of Health (MoH). Children were defined as those aged ≤ 14 years, and adults and adolescents as those aged >14 years. The model assumed (a mean of) 29,51 kg of body weight for children and (a mean of) 71,59 kg of body weight for adults and teenager patients based on the demographic characteristics extracted from the Brazilian Institute of Geography and Statistics - IBGE estimates for general population.[20] Drug costs were derived from the last contracts signed with the MoH for the provision of both bypassing agents.[21-22]

We assessed the cost differences with the bypassing usage for prophylaxis and on-demand treatment in patients with hemarthrosis episodes. For this, the model considered the minimum and the maximum dosage regimens, in which not only the dose itself was changed but also the frequency of administration of APCC and rFVIIa according to the type prescribed (prophylaxis or on-demand treatment). The minimum doses adopted were: i) prophylaxis APCC 75 U/kg 3 times a week[8], ii) on-demand APCC 75 U/kg 1 application[3,11], iii) prophylaxis rFVIIa 90 μg/kg 3 times a week[8]; iv) on-demand rFVIIa 90 μg/kg 2 applications.[3,11] And for the maximum doses, the values were: i) prophylaxis APCC 75 U/kg 4 times a week (every other day)[20], ii) on-demand APCC 100 U/kg every 12 hours (total 200U/kg) for 5 days[11,22], iii) prophylaxis rFVIIa 90 μg/kg 7 times a week[20]; iv) on-demand rFVIIa 90 μg/kg 3 doses (total 270 μg/kg) for 5 days.[8,11] In the on-demand case, it was considered a mean of 26,2 bleeding events per year.[23] The total drug cost was calculated as annual cost with prophylaxis and annual cost with on-demand at maximum and minimum dosages.

We validated the inputs with a hemophilia specialist concerning severity classification of severity bleeding events, dosage and frequency of bypassing agents' administration.

Budget Impact Model - BIM

A budget impact model was developed to estimate the potential economic impact of increasing the market share of APCC and diminishing the market share of rFVIIa as a prophylactic and on-demand treatment for patients with hemophilia A with inhibitors in Brazil. The analysis was developed from the Brazilian MoH perspective with a 5-year time frame.

Model inputs for dosing, treatments and costs were based on the CMA model. Only direct costs with medication were included. All costs are expressed in reais (BRL), and the model was developed using Microsoft Excel®.

Model Inputs

The model considered scenarios (base and best case) in which both bypassing agents are offered at SUS with different market shares (**Table S1**). To establish the market share, the base case considered the latest WFH consumption data[3] with the two agents and the best case considered Astermark and colleagues' data, which is provided by The FENOC study, an open label, randomized, crossover, equivalency trial.[24] The eligible patient population consisted of inhibitor's hemophilia A adults, adolescents and children receiving bypassing agents episodic or prophylactic treatment regimens. A measured demand approach was taken to estimate the cohort population size each year. Consumption data of both medications were used, according to Brazilian MoH hereditary coagulopathies historical data[25-28] to estimate the budget impact in these different scenarios (**Table S2**). Data from the years 2015 to 2020 were considered. Data from 2020 and 2021 were excluded from the analysis because it could introduce a bias due to the COVID-19 pandemic scenario. The population projection for future years analyzed (**Table S3)** was estimated from the trend function in the Excel®.

The proportion of patients with hemophilia A with inhibitors who were on prophylactic treatment was assumed to be 55,6% based on the real-world data on safety and effectiveness of CCPA.[18] Thus, the proportion of patients on on-demand treatment was 44,4%.

The result of the model was the relative annual cost difference between prophylaxis and on-demand treatments with both treatments. Furthermore, the model assumed 100% compliance with both regimens.

Sensitivity analysis for both models

Trying to minimize the effects of uncertain parameters in the cost-minimization and the budget impact analysis, one-way sensitivity analyses were performed. Sensitivity analyses tested the model's robustness by varying probabilities and resource use values in the model to determine how they affected the economic impact of APCC compared with rFVIIa.

Thus, tests were used to determine whether the results were affected by changes in patients' bodyweight evaluated, frequency of administration per week, dosing treatment regimen, or pricing of drugs in CMA. For BIM, the drugs acquisition and administration costs as well as the proportion of consumption according to the type of usage prescribed, for prophylaxis and on-demand treatment, were considered. All inputs were varied according to confidence interval (when available) or by ±20% to assess model robustness.

Results

Cost minimization analysis – CMA

Prophylaxis treatment analysis

According to the **minimum dose** treatment regimen, a total of 16,108 U of APCC and 19,330 mcg of rFVIIa for adults and adolescents, and 6,639 U of APCC and 7,966 mcg of rFVIIa for children would be used as a prophylactic treatment per week. For adults and adolescents, these could represent an annual cost of BRL 2,495,242 for APCC and BRL 2,596,207 for rFVIIa. For children, these could achieve BRL 1,028,872 for APCC and BRL 1,070,483 for rFVIIa (**Table 1**).

On the other hand, regarding the scenario in which the **maximum dose** usage is necessary for adult and adolescents' prophylaxis, the cost of treatment with APCC represents BRL 3,325,894 versus BRL 6,056,692 with rFVIIa, and the incremental cost difference could achieve BRL 2,730,798 (**Table 2**). **Figure 1** summarizes the results with both scenarios **minimum and maximum dose** usage.

Table 1. Base case (minimum dosage.): Inputs for **prophylaxis** with bypassing agents during immunotolerance treatment with minimum dosage.

Parameter	Children		Adults and teenagers		Source
	rFVIIa	APCC	rFVIIa	APCC	
Recommended dose	90 mcg	75 U	90 mcg	75 U	(8)
Applications per week	3	3	3	3	(8)
Dose per week	7,966 mcg	6,639 U	19,330 mcg	16,108 U	Calculated
Price per mcg or U	BRL 2.575 / mcg	BRL 2.97 / U	BRL 2.575 / mcg	BRL 2.97 / U	(24)
Annual cost of treatment - Purchase of medication	BRL 1,069,640.29	BRL 1,028,029.10	BRL 2,595,363.83	BRL 2,494,398.89	Calculated
Number of administrations per year	156	156	156	156	Calculated
Cost of each administration	BRL 5.39	BRL 5.39	BRL 5.39	BRL 5.39	(37)
Annual cost of treatment	BRL 1,070,483.44	BRL 1,028,872.25	BRL 2,596,206.98	BRL 2,495,242.04	Calculated

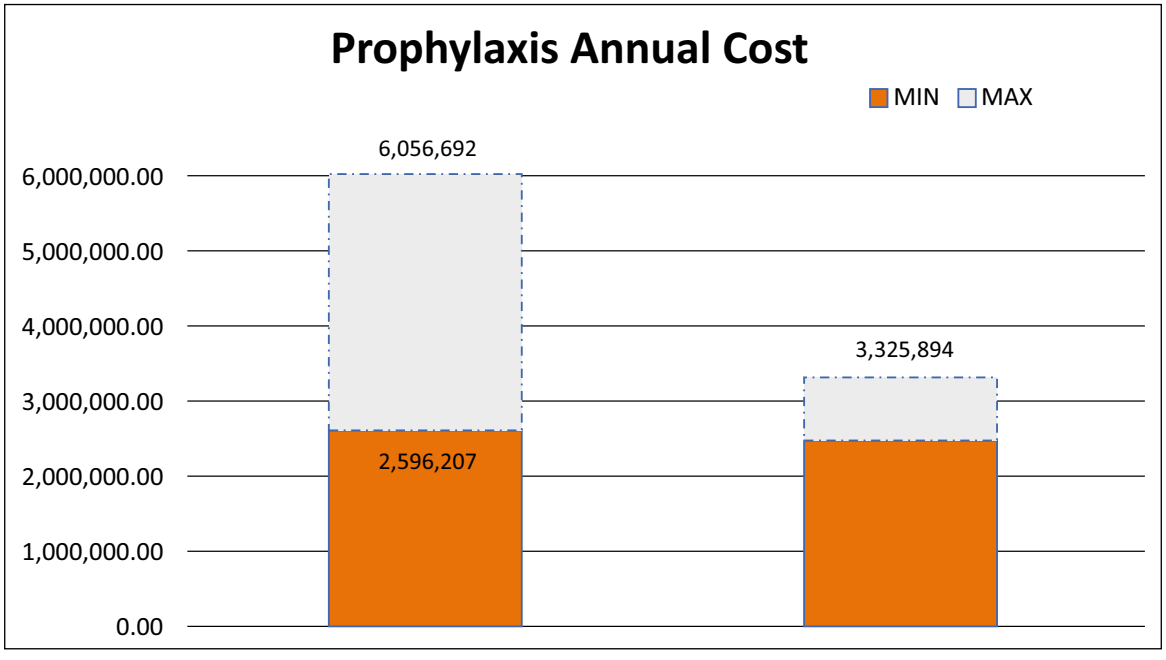
APCC - activated prothrombin complex concentrates; rFVIIa - Recombinant activated factor VII.

Table 2. Base case (minimum dosage): Inputs for **on-demand** treatment with minimum dosage.

Parameter	Children		Adults and teenagers		Source
	rFVIIa	APCC	rFVIIa	APCC	
Required dose	90 mcg	75 U	90 mcg	75 U	(8,11)
Required amount of mcg or U per event	2,655 U	2,213 U	6,443 U	5,369 U	Calculated
Total dose required considering treatment time, patient weight and average of events in 1 year	139,148 mcg	57,978 U	337,626 mcg	140,678 U	Calculated (38,39)
Price per mcg or U	BRL 2.575 / mcg	BRL 2.97 / U	BRL 2.575 / mcg	BRL 2.97 / U	(23)
Annual cost of treatment	BRL 358,305.07	BRL 172,183.14	BRL 869,387.63	BRL 417,783.34	Calculated

APCC - activated prothrombin complex concentrates; rFVIIa - Recombinant activated factor VII.

Figure 1. Annual cost for prophylaxis treatment with minimum (orange) and maximum (grey) doses of rFVIIa and APCC (BRL)



Concerning children, the cost of annual prophylactic treatment could represent BRL 1,370,735 for APCC and BRL 2,496,670 for rFVII. In addition, for hemarthrosis treatment the annual cost could represent BRL 2,295,775 for APCC and BRL 2,687,288 for rFVII. These situations could promote an annual cost reduction of BRL 391,513 and BRL 1,125,936, respectively.

On-demand treatment analysis

A total of 5,369 U of APCC and 6,443 mcg of rFVIIa would be used per hemarthrosis event to treat adults and adolescents with **minimum dosage** regimen. The costs for annual on-demand treatment in these cases would be BRL 417,783 for APCC and BRL 869,388 for rFVIIa, corresponding to a capacity of annual saving of BRL 451,604 when APCC's market share is greater than rFVIIa's.

When considering the scenario of the **maximum dosage** regimen required to treat an hemarthrosis in the same population, a total of 1,875,701 U of APCC and 9,791,162 mcg of rFVIIa would be used. The costs for these annual on-demand treatments could be BRL 5,570,445 and BRL 6,520,407, respectively, which represents a saving of BRL 949,963 when using APCC in a greater market share than rFVIIa. **Figure 2** summarizes the results with **minimum and maximum dosage** regimens.

One-way Sensitivity Analysis (OWSA)

The sensitivity analysis showed that the CMA model was more sensitive to both the changes in cost and the applied dose for on-demand treatment with rFVIIa than changes in the same parameters related to APCC. Prophylaxis dose parameters for both drugs had less impact on the model. Even though rFVIIa cost or dose used were reduced by 20%, the savings by using APCC instead of rFVIIa would be observed. **Figure 3** summarizes the results of one-way sensitivity analysis using a tornado diagram.

Figure 2. Annual cost for on-demand treatment with the minimum (orange) and the maximum (grey) doses of rFVIIa and APCC (BRL)

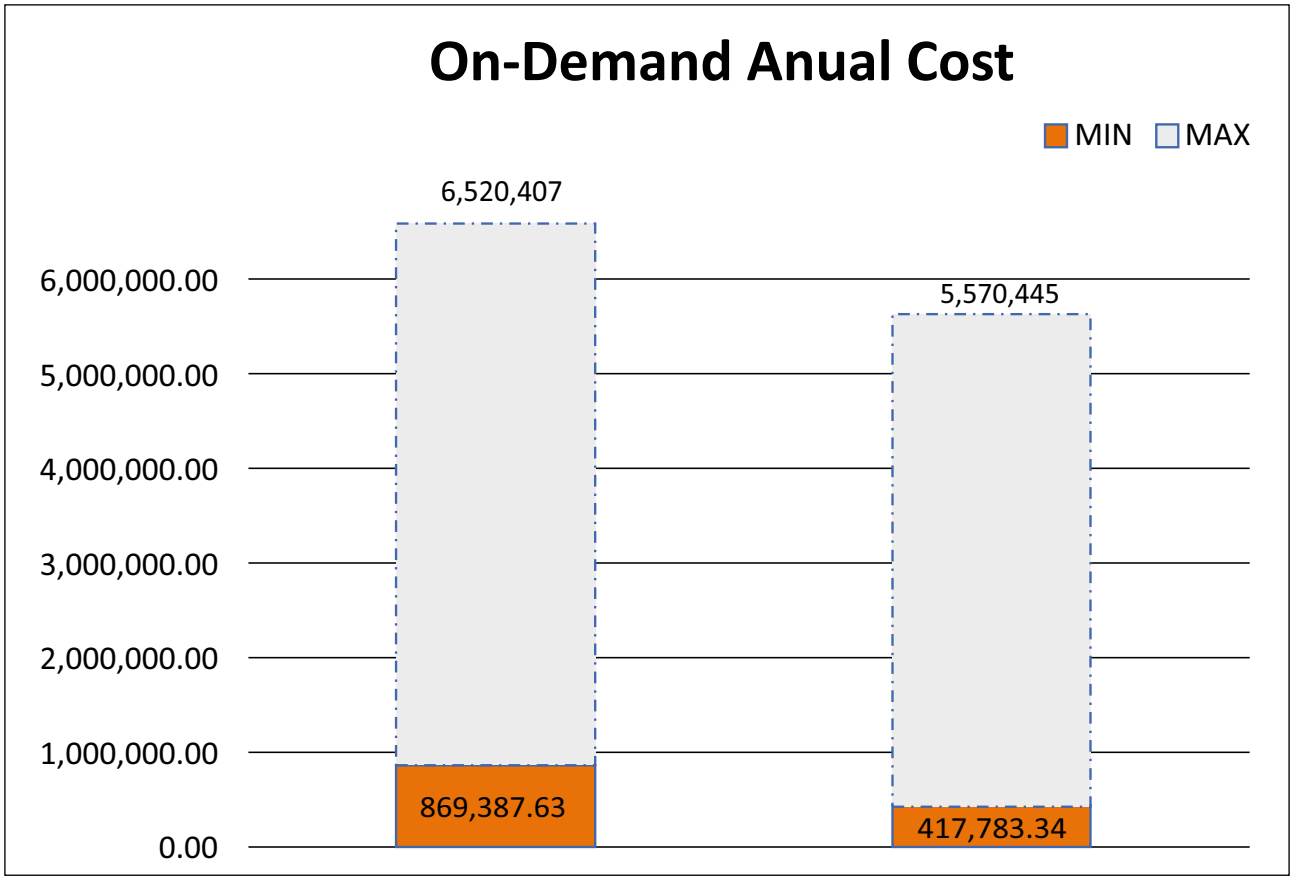


Figure 3. Results of the CMA one-way sensitivity analysis presented with a tornado chart (BRL)

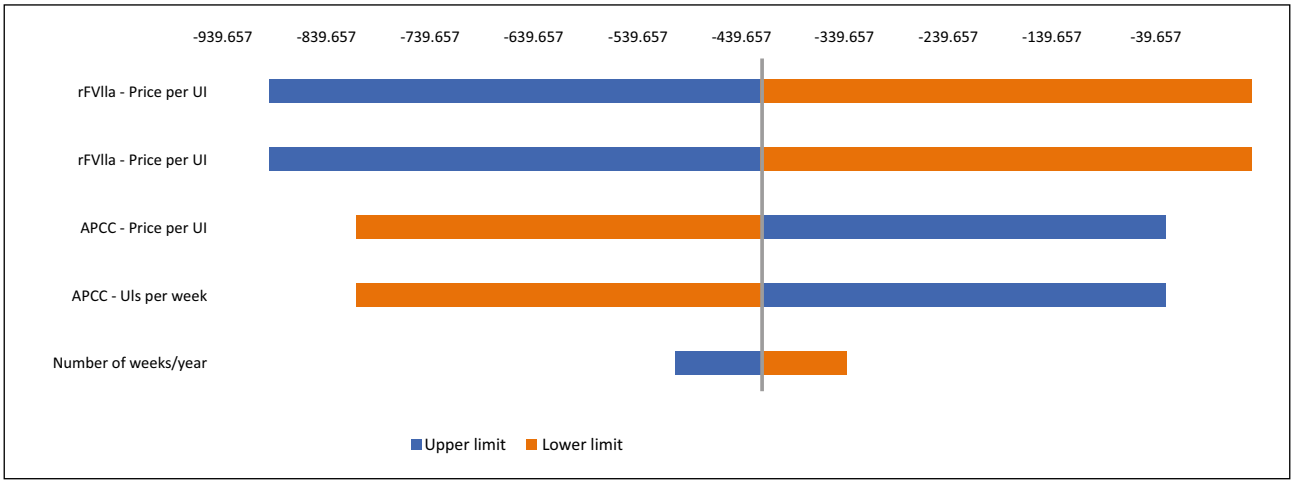


Fig. 3. CMA Tornado diagram of one-way sensitivity analysis. The incremental cost of rFVIIa vs. APCC in Brazilian reais is shown on the x-axis. For each parameter examined, the upper and lower limits of the sensitivity analysis (labels appear at either end of each band) are based on either ± 20% of the base-case, or clinically reasonable range. rFVIIa, recombinant factor VIIa; APCC, activated prothrombin complex concentrates.

Budget Impact Model – BIM

Prophylaxis treatment analysis

The market share was stablished based on the latest WFH consumption data[3] for the two agents, with a tendency of reduction of the aPCC. For the best-case scenario, it was considered the Astermark and colleagues' data, based on the FENOC study.

Considering the results of applying the **minimum values** described in **Table 1** for prophylactic treatment**,** the BIM estimated that 5 years after the partial substitution of rFVIIa, the **main use** of APCC brings the potential saving of BRL 201,622,888 – considering adults treatment. For children, these values could be BRL 83,095,850**.** These results represent a 14% budget decrease in 5 years to the public payer **(Table 3)**.

Table 3. Adults and children prophylaxis treatment Incremental Budget Impact - per year and total

Adults				
Year	**Best case**	**Base case**	**Incremental budget impact**	**Total over years**
1	290,668,473.72	292,527,714.90	-BRL 1,859,241.18	-BRL 1,859,241.18
2	269,605,540.84	325,147,260.93	-BRL 55,541,720.09	-BRL 57,400,961.27
3	247,138,412.44	298,955,059.68	-BRL 51,816,647.24	-BRL 109,217,608.51
4	226,075,479.56	274,302,344.45	-BRL 48,226,864.90	-BRL 157,444,473.41
5	203,608,351.16	247,786,765.70	-BRL 44,178,414.54	-BRL 201,622,887.95
Total over 5 years			**-BRL 201,622,887.95**	
Children				
1	119,851,699.28	120,617,957.65	-BRL 766,258.37	-BRL 66,258.37
2	111,166,793.53	134,057,480.64	-BRL 22,890,687.11	-BRL 23,656,945.48
3	101,902,894.07	123,258,348.26	-BRL 21,355,454.19	-BRL 45,012,399.67
4	93,217,988.33	113,093,967.55	-BRL 19,875,979.22	-BRL 64,888,378.89
5	83,954,088.86	102,161,559.98	-BRL 18,207,471.11	-BRL 83,095,850.00
Total over 5 years			**-BRL 83,095,850.00**	

Market share: for the base case: APCC: year 1: 54%, year 2: 53%, Year 3: 51%, Year 4: 49%, Year 5: 47%; rFVIIa: year 1: 46%, year 2: 47%, year 3: 49%, year 4: 51%, year 5: 53%; for the best-case: year: 1-5, APCC: 70% and rFVIIa: 30%

Using APCC at the **maximum dosage** regimen during prophylaxis, the savings are equal to BRL 453,170,561 if compared to adults' treatment and BRL 183,316,427 if compared to children's therapy.

On-demand treatment analysis

Regarding the on-demand adult usage with the **minimum dosage**, the amount saved could be BRL 42,696,097 after 5 years partial substitution of rFVIIa for APCC (**Table S4**). For children, these values could be BRL 17,596,556 (**Table S5**). These results represent 2,85% budget decrease in 5 years to the public payer.

However, concerning the **maximum dosage** treatment, the total budget for the population with hemophilia A with inhibitors would represent a saving of BRL 322,680,907 and of BRL 132,988,097 for public payer, depending on the strata population analyzed, adults or children, respectively.

In both situations, the budget required for treatment (on-demand or prophylactic) is lower after the partial substitution of rFVIIa to APCC, increasing its market share.

One-way Sensitivity Analysis (OWSA)

We observed that the prophylactic costs with rFVIIa and APCC are responsible for most of the cost saved in 5-years horizon, followed by the proportion of patients considering on-demand treatment. However, the proportion of patients on prophylaxis is the parameter that least impacts the model (**Figure 4**).

A one-way sensitivity analysis demonstrated that the direction of the results was not altered by a 20% increase or decrease in the cost of treatment or consumption proportion of either APCC or rFVIIa. The cost savings realized by using most of the market share of APCC instead of rFVIIa would range from BRL105,580 to BRL67,514.

Concerning on-demand treatment analysis, the main costs that can influence the cost saved in 5-years horizon is the same as the other model. However, the difference is on rFVIIa on-demand costs and on-demand consumption proportion, which has the third and the fourth position at the tornado diagram. Similar to OWSA prophylaxis treatment, the proportion of patients on prophylaxis is the parameter that least impacts the model (**Figure 5**).

Figure 4. Prophylactic treatment: Results of the BIM one-way sensitivity analysis presented with a tornado chart (BRL)

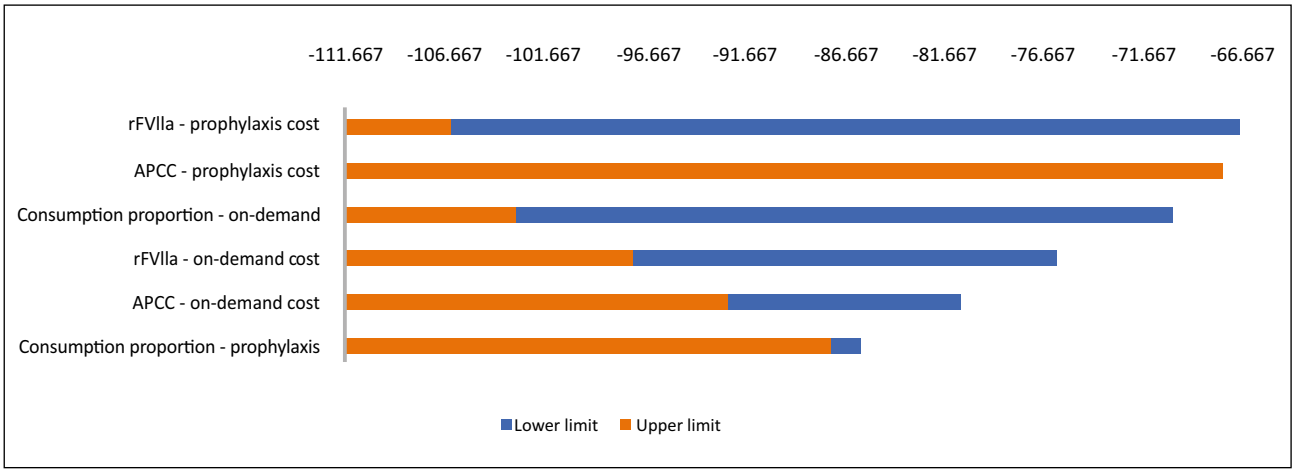


Fig. 4. BIM Tornado diagram of one-way sensitivity analysis for prophylactic treatment. The incremental cost of rFVIIa vs. APCC in Brazilian reais is shown on the x-axis. For each parameter examined, the upper and lower limits of the sensitivity analysis (labels appear at either end of each band) are based on either ± 20% of the base-case, or clinically reasonable range. rFVIIa, recombinant factor VIIa; APCC, activated prothrombin complex concentrates.

Figure 5. On-demand treatment: Results of the BIM one-way sensitivity analysis presented with a tornado chart (BRL)

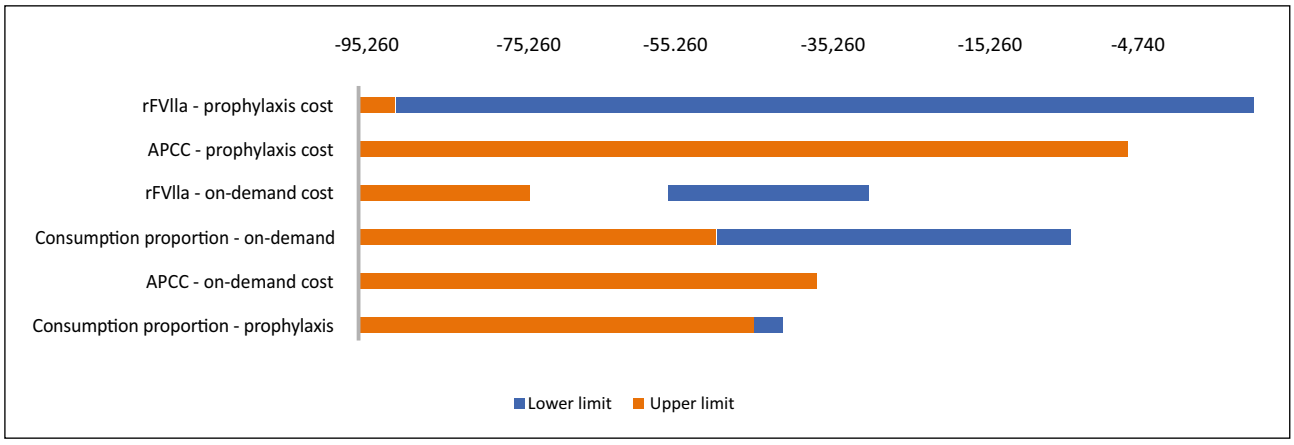


Fig. 5. BIM Tornado diagram of one-way sensitivity analysis for on-demand treatment. The incremental cost of rFVIIa vs. APCC in Brazilian reais is shown on the x-axis. For each parameter examined, the upper and lower limits of the sensitivity analysis (labels appear at either end of each band) are based on either ± 20% of the base-case, or clinically reasonable range. rFVIIa, recombinant factor VIIa; APCC, activated prothrombin complex concentrates.

Discussion

Treat and prevent bleeding episodes in high titer inhibitors hemophilia A patients with bypassing agents are described in the SUS guidelines. The available rFVIIa and APCC promote increase on quality of life. Despite the benefits, bypassing treatment is costly and time-consuming concerning posology and the nature of infusions.[29,30]

The model presented here demonstrated the cost difference between APCC and rFVIIa usage. The cost per patient for prophylactic and on-demand treatments is estimated to be lower with APCC than in rFVIIa usage, in general. Regardless of the population adopted in the analysis, both adult or pediatric, the results showed that the cost per patient for episodic treatments is estimated to be higher with rFVIIa than in APCC usage with the minimum dosage, which can achieve almost half of the cost with the other product. However, when considering the maximum dose usage, this difference is not so expensive. On the other hand, for prophylactic treatment, the scenario is the opposite. Regarding the maximum dose usage, the cost of treatment with APCC represents approximately half of the cost of prophylaxis with rFVIIa and with the minimum dose, the incremental cost difference is less expensive.

These differences could be explained by the number of necessary doses with each treatment (an average of 2 with rFVIIa vs 1 with APCC for on-demand treatment at the minimum dose, for example). However, considering both therapeutic usages, the APCC could significantly decrease the total drug cost, which can promote different cost savings scenarios over the 5 years period analyzed, regardless of the treatment purpose, therapeutic regimen, and patient age.

This remained robust even if the rFVIIa cost or dose used were reduced by 20% in a 1-way sensitivity analysis, the savings by using APCC instead of rFVIIa would be observed.

Several studies had compared costs or cost-effectiveness of APCC and rFVIIa in hemophilia inhibitor patients, some of which are about treating mild-to-moderate bleed.[30-33] One study conducted in USA assessed the treatment costs when patients undergo major orthopaedic surgeries, such as knee or hip arthroplasty, considering 3 possible scenarios: (i) APCC used in the pre/intra-operative periods and postoperative ones; (ii) rFVIIa used in all periods; and (iii) rFVIIa used during pre/intra-operative phase and APCC in the second one. The model demonstrated that the use of APCC alone or in combination with rFVIIa has emerged as a cost-saving approach. The APCC exclusive usage could decrease

total drug cost by 58% and save over $470,000 per surgery over the entire perioperative period (14-day). The sequential use of both bypassing agents would increase total drug cost by 9% when compared with APCC scenario but would remain more than 40% lower than the rFVIIa exclusive use.[16] Another study realized a cost-minimization analysis from a US third party payer perspective. It showed the total medical cost to treat a bleed with APCC or rFVIIa as first-line therapy/medication was US$ 25,969 and US$ 35,838 – respectively, in order the APCC use saves US$9,869 per mild-to-moderate bleed.[34] Other model compared the costs of bypassing agents in the initial home treatment of minor hemarthrosis episodes in a child with high-titre inhibitors from a societal perspective. The study found the APCC treatment would result in a mean cost per episode of $21,000 compared with $33,400 for rFVIIa.[31]

On the other hand, a cost-effectiveness model from the Spanish National Healthcare System perspective found the opposite. When rFVIIa is compared to APCC to treat mild-to-moderate joint bleeding episodes in severe hemophilia A patients with high-titre and high-responding inhibitors, rFVIIa was shown as an advantage option compared with APCC. The mean cost per bleed was estimated at €8,473 and €15,579 in children and adults, respectively, treated with rFVIIa vs. €8,627 and €15,677 in both subgroups treated with APCC.[31] Other cost-effectiveness study among adults with high-titre, high responding inhibitors found similar results to the previous one, in which rFVIIa treatment was found as the dominating option. This modelling was performed from the perspective of the UK's National Health Service (NHS). The expected cost of managing a minor bleeding event following initial treatment with rFVIIa and APCC was estimated to be £11,794 and £20,467 – respectively, and the expected time to resolving it would take almost twice as long using APCC instead of rFVIIa.[30]

Our results differ from these two cost-effectiveness studies.[30,33] Parts of the disparities between our findings and these studies are explained by the different efficacy assumption used in those analysis. In the first one[33], it was considered a higher percentage of patients responding to rFVIIa within 24 hours (for APCC: 52.7% resolved bleed without rebleed, 9.3% resolved bleed with rebleed and 6.3% switched bypassing agent after 24h; for FVIIa, the numbers are: 78.4%, 13.2% and 1.3%, respectively). According to the authors, this was based on published data[30,32] and expert opinion. And the second study assumed favors efficacy of rFVIIa, based on two single-arm observational studies (79% APCC efficacy[34] vs. 92% rFVIIa efficacy[32]). It is important to note that these cost-effectiveness studies didn't consider that the two bypassing agents had similar efficacy of different treatment regimens, shown by two head-to-head clinical trials and confirmed by a Cochrane's group systematic review.[12,35,36] The FEIBA NovoSeven comparative (FENOC) study[35] compared one dose of APCC (75–100 U/kg) with two doses of rFVIIa (90–120 μg/kg) and no statistically significant difference within 48h follow-up was found. And a study developed by Young and cols.[36] showed no difference between patients using one dose of 75 U/kg APCC and patients using three doses of 90 μg/kg rFVIIa. One of the limitations of this modelling is that it only took into consideration the direct costs associated with bypassing agents used. Additional direct costs, including reducing other treatments consumption or costs related to adverse effect management, as well as indirect costs, such as decreased productivity, were not considered for these analyses since the study reflects the Brazilian Universal Public Healthcare System perspective and not society's perspective. Further analysis could be done to test whether the reduced overall healthcare costs will be kept. An additional potential limitation concerns our choice of a hemarthrosis as the event of the bleeding in the on-demand clinical scenario. Despite this, there was great consistency between the literature and the expert opinions for dosing values for both agents.[2] The clinical optimal number of doses used to resolve a bleeding is the key driver of total medical cost.[32] Much of the uncertainty associated with cost estimates in hemophilia stems from the clinical variability around treating the disease.[33] On the other hand, this is the only study which evaluated simultaneously both the on-demand and prophylaxis use of bypassing agents, showing that the cost savings are observed for both treatment situations. And the sensitivity analyses did not change the selection of APCC as the economically preferred

strategy. So, this study suggests that, with all the other parameters maintain the same/ being equal, APCC represents a cost saving alternative to payers. This advantage can provide value from the patient and payer's perspective because when substituting rFVIIa for APCC in a part of the market, it allows that with the same budget initially spent on the base scenario, more patients can be treated in the alternative scenario, regardless of whether the use is on-demand or prophylaxis. Thus, this cost savings from using APCC could translate into the ability to provide more care on inhibitor patients in need of treatment without increasing resource constraints on the healthcare system.

Conclusion

The analysis suggests a potential cost saving from Brazilian National Healthcare System [SUS] perspective by using APCC instead of rFVIIa for hemophilia A patients with inhibitors, mainly concerning prophylaxis. The results are important for the Brazilian Public Healthcare System and could provide guidance for resource allocation, improving clarity in decision making for inhibitor bypass agents' usage in this context, considering the patient clinic response.

Authors' contributions
CMSP, ALSS, FC, JS, TBR e GVB: responsible for the design of the study and made critical revisions of the manuscripts. All authors were responsible for data collection, analysis and drafted the manuscript. All authors read and approved the final manuscript, ensuring the accuracy and integrity of the entire work.

Conflicts of interest
CMSP received honoraria from providing consultancy for Takeda, NovoNordisk, Pfizer and Bayer. JS, TR, FC and ALS are Takeda Pharmaceuticals, São Paulo, Brazil employees. GVB is IQVIA Solutions do Brasil Ltda., São Paulo, Brazil employee.

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Data Availability Statement
The data is available on demand from the reviewers and after publication, the underlying data will be available upon formal request to the authors.

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SUPPLEMENTARY MATERIAL

Table S1. Market share scenarios: base and best case

Base case	ANO 1	ANO 2	ANO 3	ANO 4	ANO 5	Source
APCC	54%	53%	51%	49%	47%	Calculated market share based on WFH 2021 data (3)
rFVIIa	46%	47%	49%	51%	53%	
Best case*	**ANO 1**	**ANO 2**	**ANO 3**	**ANO 4**	**ANO 5**	**Source**
APCC	70%	70%	70%	70%	70%	Based on Aster mark, 2007 (35)
rFVIIa	30%	30%	30%	30%	30%	

*** rFVIIa 's smaller market share**

Table S2. Eligible patients with hemophilia A, consumption data for partially activated prothrombin complex and recombinant activated coagulation factor VII in Brazil.

Parameter	Data	Source
Partially activated prothrombin complex (APCC) consumption		
APCC consumption in patients with inhibitor titers ≥ 5 UB/ml in Brazil (2015)	197	Hereditary Coagulopathies Data
APCC consumption in patients with inhibitor titers ≥ 5 UB/ml in Brazil (2017)	183	
APCC consumption in patients with inhibitor titers ≥ 5 UB/ml in Brazil (2018)	177	
APCC consumption in patients with inhibitor titers ≥ 5 UB/ml in Brazil (2019)	160	
APCC consumption in patients with inhibitor titers ≥ 5 UB/ml in Brazil (2020)	137	
Recombinant activated coagulation factor VII (rFVIIa) consumption		
rFVIIa consumption in patients with inhibitor titers ≥ 5 UB/ml in Brazil (2015)	128	Hereditary Coagulopathies Data
rFVIIa consumption in patients with inhibitor titers ≥ 5 UB/ml in Brazil (2017)	129	
rFVIIa consumption in patients with inhibitor titers ≥ 5 UB/ml in Brazil (2018)	121	
rFVIIa consumption in patients with inhibitor titers ≥ 5 UB/ml in Brazil (2019)	118	
rFVIIa consumption in patients with inhibitor titers ≥ 5 UB/ml in Brazil (2020)	102	

Table S3. Estimated number of patients with hemophilia A and inhibitors who can use bypassing agents in the analyzed years

	ANO 1	ANO 2	ANO 3	ANO 4	ANO 5	Source
APCC	112	101	90	79	68	Calculated based on trend function with previous years data (2015 – 2019) consumption (25–28)
rFVIIa	95	91	86	82	77	

Table S4. Adults on-demand treatment Incremental Budget Impact - per year and total

Year	Best case	Base case	Incremental budget impact	Total over years
1	341,517,918.93	350,018,127.65	-BRL 8,500,208.71	-BRL 8,500,208.71
2	316,770,243.65	325,147,260.93	-BRL 8,377,017.28	-BRL 16,877,226.00
3	290,372,723.34	298,955,059.68	-BRL 8,582,336.33	-BRL 25,459,562.33
4	265,625,048.06	274,302,344.45	-BRL 8,677,296.40	-BRL 34,136,858.73
5	239,227,527.76	247,786,765.70	-BRL 8,559,237.94	-BRL 42,696,096.67
Total over 5 years			**-BRL 42,696,096.67**	

Market share: for the base case: APCC: year 1: 54%, year 2: 53%, Year 3: 51%, Year 4: 49%, Year 5: 47%; rFVIIa: year 1: 46%, year 2: 47%, year 3: 49%, year 4: 51%, year 5: 53%;
for the best-case: year: 1-5, APCC: 70% and rFVIIa: 30%

Table S5. Children on-demad treatment Incremental Budget Impact - per year and total

Year	Best case	Base case	Incremental budget impact	Total over years
1	140,808,535.65	144,311,769.21	-BRL 3,503,233.56	-BRL 3,503,233.56
2	130,605,018.57	134,057,480.64	-BRL 3,452,462.06	-BRL 6,955,695.63
3	119,721,267.03	123,258,348.26	-BRL 3,537,081.23	-BRL 10,492,776.86
4	109,517,749.95	113,093,967.55	-BRL 3,576,217.60	-BRL 14,068,994.45
5	98,633,998.40	102,161,559.98	-BRL 3,527,561.57	-BRL 17,596,556.03
Total over 5 years			**-BRL 17,596,556.03**	

Market share: for the base case: APCC: year 1: 54%, year 2: 53%, Year 3: 51%, Year 4: 49%, Year 5: 47%; rFVIIa: year 1: 46%, year 2: 47%, year 3: 49%, year 4: 51%, year 5: 53%; for the best-case: year: 1-5, APCC: 70% and rFVIIa: 30%