Cost-effectiveness of emicizumab versus by-passing agents in patients with haemophilia A and FVII inhibitors in France

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INTRODUCTION

- Hemophilia A is a **rare genetic disease** affecting approximately 6,000 French patients in 2018[1]. The development of an anti-FVIII inhibitor is the most serious complication of hemophilia A. It occurs in up to 30% of severe hemophiliac patients and in 5 to 10% of minor/moderate patients[2].
- The current management of hemophilia A with bypassing agents (BPAs) represents a significant therapeutic burden and a limited adherence to BPAs in practice[3,4]. **Emicizumab (Hemlibra®) is the first monoclonal antibody developed in hemophilia A**. On February 23th 2018, it obtained a Marketing Authorization for the prevention of bleeding episodes in hemophilia A patients who have developed an anti-FVIII inhibitor and it is officially reimbursed in France for this indication since February 7th 20195. As part of its registration on the list of products reimbursed by Health Insurance, emicizumab has been evaluated by the French National Authority for Health (HAS): the Transparency Commission (TC) has allocated a important therapeutic value (SMR) and an important added therapeutic value (ASMR II). A medico-economic analysis, based on the price requested by the laboratory, has also been evaluated by the Commission Evaluation Economic and Public Health (CEESP).
- The purpose of this analysis is to evaluate **the efficiency of emicizumab in France** compared to the current management by BPAs in patients with hemophilia A and anti-FVIII inhibitors and not covered by an immune tolerance induction protocol (ITT), at the final published tariff.

MATERIEL AND METHODS

- The methodology of cost-utility analysis (cost per QALY) and cost-effectiveness (cost per bleeding) was validated by the CEESP in its report of October 9th 20186. It was based on a two-health states (live, dead) Markov model over a time horizon of 5 years and from a collective perspective. Deterministic and probabilistic sensitivity analyses were performed.
- **Emicizumab was compared with current management by BPA (aPCC and rFVIIa) in prophylaxis or on demand** according to their real-life use in the FranceCoag cohort. The distribution of therapeutic scheme was: 33% for prophylaxis BPA and 67% for BPA on demand.
- Based on available data, the analysis was restricted to patients for whom an ITT protocol was not considered or was not effective, representing 82% of the population of the indication.
- The model inputs (Table 1) were mainly those of the HAVEN 1[7] trial (utility, bleeding rate, amount of treatment consumed) that compared emicizumab to BPA on demand, and from an indirect comparison for prophylaxis with BPAs. The price of emicizumab used in the analysis is the final price fixed by the French Economic Committee of Health Products at the end of 2018.

Table 1: Main inputs of the model

	Emicizumab	Prophylaxis with BPA	BPA on demand	Source
Prophylaxis treatment				
Cost per unit	77.13 €/mg	0.903 €/UI (aPCC) 0.608 €/µg (rFVIIa)		Price on 2018 december / NIS BH28768
Dose per injection	3 mg/kg/week (4 weeks of induction) 1,5 mg/kg/week (maintenance)	99,44 UI/kg 3x/sem (aPCC – 71.4%) 90 µg/kg/j (rFVIIa – 28.6%)	-	European SPC / NIS BH28768
Product loss	All ages : 17.1% [0-11] years : 45.0% [12-17] years : 9.3% [18-inf] years : 7.2%			Optimization of doses according to mean weight per age (INSEE)
Bleeding management				
Number of bleeding per year	2.9	8.1	23.3	HAVEN 1
Distribution				
aPCC	57.7%		27.1%	HAVEN 1
rFVIIa	30.8%		57.3%	
aPCC + rFVIIa	11.5%		15.6%	
Dose per bleeding				
aPCC	128 UI/kg		132 UI/kg	HAVEN 1
rFVIIa	281 µg/kg		296 µg/kg	
aPCC + rFVIIa	174 UI/kg + 309 µg/kg		319 UI/kg + 718 µg/kg	
Administration				
Cost per nurse visit	30.6€ (visit of a nurse for 20% of the injections)			
Adverse events				
Hospitalisations (Annual occurrence rate / cost)				
Thrombotic Microangiopathy)	6.19% / 3,568 €	--		HAVEN 1 / PMSI
Skin necrosis	6.19% / 6,898 €	--		
Superficial thrombophlebitis	6.19% / 2,517 €	--		
Device-related infection	--	12.04% / 6,625 €		
Device-related scepticemia	--	12.04% / 6,625 €		
Urinary tract infections	--	12.04% / 3,334 €		
Ambulatory cares				
Upper respiratory tract infection	43.33% / 31 €	36.11% / 31 €		
Nasopharyngitis	6.19% / 31 €	24.07% / 31 €		
Reaction/allergy on the injection site	49.52% / 7 €	--		
Hospitalisations				
Number of days of hospitalisation	4.1 days		9.1 days	HAVEN 1
Cost per day of hospitalisations	489.64			PMSI
Costs of follow up				
Annual cost				
Utility				
Utility	0.7683	0.5697		HAVEN 1

*: Medical visits, medical procedures, other health professionals, drugs not reimbursed, alternative medicine, Medical Device, transportations (source: CHESS study[8])

RESULTS

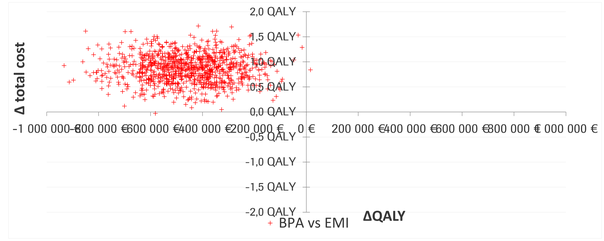
- Emicizumab in prophylaxis is a dominant strategy in children and adult patients as it is more effective and less expensive than the current strategy by BPA in prophylaxis or on demand (Table 2).
- Over 5 years, the mean total cost per patient was 2,3 M€ in patients treated with emicizumab, versus 2,7 M€ with BPA, associated to 3,3 and 2,4 QALYs respectively. Thus, emicizumab brings 0,9 additional QALYs per patients for a saving of almost 426 000€.

Table 2: Results of the base-case analysis

	Emicizumab	Standard treatment (BPA)	Incremental
Years of life gained (total)	4.5	4,5	
QALYs (total discounted)	3.3	2.4	**0.88**
Bleeding (total)	13.0	81.8	**68.74**
Costs on 5 years (total)	€ 2,304,676	€ 2,730,483	**€ - 425,807**
ICER (Incremental Cost effectiveness Ratio)			**EMI dominant**

Figure 1. Probabilistic Sensitivity Analysis (PSA) scatter plot
99.8% of simulations on the probabilistic sensitivity analysis are in the Northwest of the PSA scatter plot.

Uncertainty exploration shows that Emicizumab is a dominant strategy with a 99.8% probability (Figure 1).



Extreme exploratory scenarios were analyzed, including one integrating only prophylactic BPA treatment and another only BPA treatment on demand (Table 3).

Table 3: Results of the exploratory scenario

	Emicizumab vs. Standard treatment (BPA)	
	100 % prophylaxis	100 % on demand
Incremental cost	€ - 2,986,125	€ 477,561
QALY gained	0.88	0.88
Avoided bleedings	23.33	91.56
ICER	**EMI is dominant**	**€ 541,952 /QALY**

DISCUSSION

- In addition of being an effective therapeutic alternative for the prevention of bleeding episodes (87% reduction in bleeding vs. no prophylaxis) and limiting the heaviness of treatment (a single weekly subcutaneous administration vs 3 to 7 IV administrations per week), **emicizumab is a dominant strategy** compared to by-pass agents (BPA) in France. The benefits of introducing emicizumab for this indication are important for patients, public health and economic reasons.
- This medico-economic analysis is based on the methodology validated by the HAS and on the published final price for Hemlibra®.
- These results are conservative as the potential impact of emicizumab on the reduction of arthropathy progression, mortality or the burden of caregivers is not taken into account.
- Medico-economic evaluation in rare diseases relies on traditional methods of evaluation which may have their limits given the lack of data, which is mainly based on the lack of data to model the consequences of the reduction of bleeding on the long-term evolution of arthropathy and disability.

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