# HEALTH TECHNOLOGY ASSESSMENT OF EMICIZUMAB FOR PEDIATRIC HEMOPHILIA A FROM A HOSPITAL PERSPECTIVE

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**HTA175**


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## INTRODUCTION

**Hemophilia A (HA)** is caused by a mutation in Factor VIII (FVIII) gene at the X chromosome (so affecting mostly males) and results in frequent **bleeding** crisis, mainly in joints, skin, mucosae and other organs. These crises require hospitalization and treatment with intravenous FVIII infusions.

A serious complication is the development of early **inhibitors** which hinder treatment response and require high-cost drugs (bypassing agents, BPA).

**Emicizumab (ECZ) subcutaneous (SC) prophylaxis** has shown to prevent bleeding episodes by promoting hemostasis, thus reducing the need for hospitalization and costs of care, and improving quality of life (QOL) in HA patients, especially children.

## OBJECTIVE

To assess effectiveness, safety and budget impact of **prophylactic ECZ** to prevent bleeding episodes in children with HA with inhibitors at a pediatric referral hospital.

**Context:** Hematology requested incorporation of ECZ in 2020 and was rejected by the **Pharmacy Committee** on high-cost grounds.

The **hospital-based Health Technology Assessment (HTA) Unit** then undertook a full assessment to review all available evidence and estimate hospital costs and budget impact.

## METHOD

HTA full report based on systematic review (SR) of the evidence, budget impact analysis (BIA) and real world data (RWD) analysis of hospital costs and effects.

Pubmed, Centre for Reviews and Dissemination (Univ. of York), Trip Database, Google Scholar and grey literature were searched (up to Dec.2020).

References from selected articles were also reviewed.

The economic evaluation (EE) used efficacy data from randomized controlled trials (RCT), local hospital costs (2020), and effectiveness from RWD (hospital databases) of children who received ECZ from their health insurance.

## RESULTS

### 1. Evidence search results:

**SR** retrieved 4 controlled trials **(HAVEN studies 1-4, Table 1)**, 3 observational studies, 9 evidence-based clinical practice guidelines and 13 EE.

ECZ prophylaxis in children with severe HA with inhibitors showed consistent evidence of safety and efficacy:

- Reduction of annual bleeding rate (ABR) in >90% (60-90% of patients free of all bleeding)
- Resolution of 100% of target joints (ABRJ)
- Removal of 50% of central venous catheters
- Improvement in QOL and school attendance.

EE from different contexts found it cost-effective and dominant compared to alternative treatment options, and even generating savings, so it is considered standard of care.

### 2. Budget impact analysis (RWD):

**Real world data analysis** of hospital patients who were receiving ECZ showed substantial reduction of general and joint bleeding episodes, less hospitalizations and use of hospital resources **(Table 2)**.

**BIA** estimated that introduction of **ECZ** prophylaxis in children with severe HA with inhibitors would generate annual hospital **savings of ARS 23.5 million (≈ USD 147000)**, mostly due to a 38% decrease of annual expenses in high-cost treatment drugs for HA.

BIA was sensitive to drug prices and basal ABR. Sensitivity analysis estimated the cost of prophylaxis with ECZ would equal the cost of ABP on demand (therapeutic) for an ABR of 21.9 (similar to HAVEN 2).

**TABLE 1: Evidence of emicizumab efficacy from HAVEN trials**

| HAVEN Study | Design | Patients' age | Sample size | SC dose frequency | Efficacy end-points |
|---|---|---|---|---|---|
| HAVEN 1<br>Oldenburg J. et al.<br>NEJM 2017 | Multicenter open phase 3 RCT<br>Prophylactic ECZ in severe HA with inhibitors vs. alternative treatments (prophylactic or therapeutic BPA) | >12 years | 109 | Weekly | <87% ABR (2.9 vs. 23.3 events)<br>63% no bleeding episodes with ECZ vs. 6% control group<br><79% intra-subject ABR<br>+21 points in QOL scores |
| HAVEN 2<br>Young G. et al.<br>Blood 2019 | Multicenter open phase 3 non-randomized CT<br>Prophylactic ECZ in children with severe HA with inhibitors with 3 different regimens | <12 years | 85 | Every 1-2-3 weeks | ABR 0.3 events/year<br>63% free of bleeding episodes & 77% no treatable bleeding episodes<br><99% intra-subject ABR vs. previous ABP<br>100% resolution of target joints (ABRJ=0)<br>49% removal of central venous lines<br>>QOL & < school absenteeism |
| HAVEN 3<br>Mahlangu J. et al.<br>NEJM 2018 | Multicenter open phase 3 RCT<br>Prophylactic ECZ in severe HA without inhibitors vs. alternative treatments (BPA) | >12 years | 152 | Every 1-2 weeks | <97% ABR (ECZ 1.3-1.5 vs. 38.2 control)<br>56 -60% free of bleeding episodes with ECZ vs. 0% control group<br><68% intra-subject ABR |
| HAVEN 4 (interim)<br>Jimenez-Yuste V et al<br>Blood 2017 | CT extension phase cohort (interim analysis results at 25 weeks) | >12 years | 41 | Monthly | ABR on ECZ 2.4 events/year<br>56% free of bleeding episodes<br>100% patient preference for ECZ |

**TABLE 2: Budget impact analysis of ECZ incorporation at hospital level (2020)**

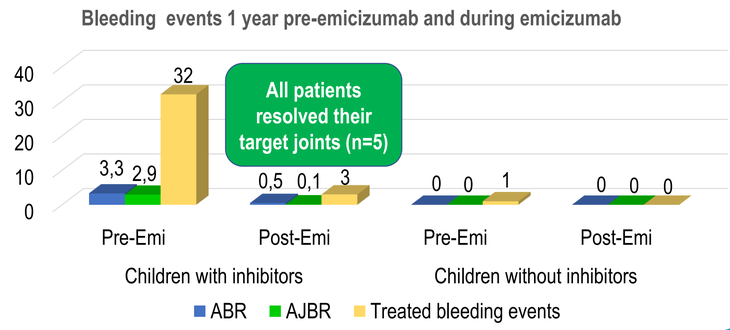
| | PRE-ECZ (82 months follow-up) | | | | POST-ECZ (20 months follow-up) | | | |
|---|---|---|---|---|---|---|---|---|
| **CLINICAL DATA AND RESOURCE USE** | **Annual/patient** | | **Annual total** | | **Annual/patient** | | **Annual total** | |
| | N°/pt./year | Cost/pt./year | Total N°/year | Total cost/year | N°/pt./year | Cost/pt./year | Total N°/year | Total cost/year |
| ABR (non-articular) | 0,98 | | 2,94 | | 0 | 0 | 0 | 0 |
| ABRJ (joints) | 2,20 | | 6,60 | | 0 | 0 | 0 | 0 |
| N° Catheter-related infections/thrombosis | 0,24 | | 0,72 | | 0 | 0 | 0 | 0 |
| HA-related hospitalization days (school days lost) | 8,98 | | 26,94 | | 0 | 0 | 0 | 0 |
| **Total hospitalization expenses** | | **$60.307** | | **$180.790** | **0** | **0** | **0** | **0** |
| **HA-SPECIFIC MEDICATION** | | | | | | | | |
| Factor VIII (Units) | 380.890 | $13.040.477 | 1.142.670 | $39.121.431 | | | | |
| FEIBA (Units) | 155.000 | $7.579.500 | 465.000 | $22.738.500 | | | | |
| Emicizumab (mg) | | | | | 2400 | $12.799.200 | 7200 | $38.397.600 |
| **Total medication expenses** | | **$20.619.977** | | **$61.859.931** | | **$12.832.324** | | **$38.397.600** |
| **TOTAL EXPENSE** | | **$20.680.284** | | **$62.040.722** | | **$12.832.324** | | **$38.397.600** |

**Estimated annual impact of ECZ prophylaxis (RWD 3 pts.) on clinical indicators and resource use:**

- Prevention of 3 general bleeding episodes
- Prevention of 7 joint bleeding episodes
- Prevention of 1 catheter-related infection
- Avoidance of 1 central venous catheter replacement
- Gain of 27 hospital bed-days and school-days

**Figure:**

**Updated 2024 data of patients on ECZ prophylaxis (Hematology, Garrahan Hospital)**




## CONCLUSIONS

The hospital Health Technology Assessment Unit report to hospital management strongly recommended introduction of ECZ prophylaxis in children with severe HA with inhibitors (and also without inhibitors but with no available venous access). The proposal was accepted and this strategy is now standard of care for this subgroup of patients. Our report was sent to Ministry of Health to promote introduction at country level.

## CONTACT INFORMATION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