Characteristics and Outcomes of Health Technology Assessment Submissions for Advanced Therapy Medicinal Products in Europe: Perspective From Non-EU$_5$ Countries

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Introduction

- Advanced therapy medicinal products (ATMPs) are innovative interventions that are based on gene therapy, somatic cell therapy, and tissue-engineered products. They often show great therapeutic potential but are typically supported by very limited clinical data and are commonly associated with substantial acquisition costs.[1,2]
- Regulatory agencies within the European Union (EU) have adapted and launched regulatory pathways to accelerate patient access to ATMPs and the adoption of these high-cost therapies by the major European economies has been extensively discussed.[3]
- Relatively little attention has been given to countries with less resilient healthcare budgets to manage the impact of the ATMP revolution while also maximising patient access.[3]
- The aim of this investigation was to review the outcomes of health technology assessment (HTA) submissions of ATMPs among a basket of non-EU5 European countries with established HTA functions to assess the extent to which these products have been adopted across the region.

Methods

- The official website of the European Medicines Agency (EMA) was reviewed to identify ATMPs with current marketing authorisation (MA).
- Countries chosen to represent the typical European environment with respect to health expenditure were Austria, Belgium, Czechia, Luxembourg, Netherlands, Poland, Portugal, and Sweden.
- Official websites of the HTA agencies of the selected countries were reviewed to identify and extract publicly available HTA reports for ATMPs.
  - HTA bodies included GÖG and HVB (Austria), KCE and RIZIV (Belgium), SKUL (Czechia), IGSS (Luxembourg), NHCI (Netherlands), AOTM (Poland), INFARMED (Portugal) and SBU (Sweden).
- Assessment criteria and final reimbursement recommendations were extracted from relevant documents where reported. Other variables of interest included time to reimbursement decision (from MA), use of a managed entry agreement and evidence development requirements.

Results

- Among the countries considered, 28 of the 82 publicly available HTA submissions of ATMPs identified resulted in a positive recommendation for general reimbursement (**Table 1**); however, across all countries most ATMPs had no information or were pending evaluation.
- The average (mean) time to a reimbursement decision (from market authorisation) was 22 [range: 4–48] months (**Table 1**).
- On average, only 3 ATMPs per country were approved for routine reimbursement; the country with the greatest number of reimbursed ATMPs was Sweden (n=6); the country with the most publicly available HTA decisions was the Netherlands (n=8) (**Table 1**).
- Among available records, the product that received the most positive reimbursement decisions across all countries was KYMRIAH® (n=6).
  - The clinical value of KYMRIAH® was deemed uncertain across the appraising agencies; however, in most instances where the final decision was to reimburse, a price agreement was made to guarantee patient access (**Table 2**).
  - For the diffuse large B-cell lymphoma indication, the negative decision rationale was anchored on substantial difficulty in assessing cost-effectiveness **(Table 2**).
- Among publicly available records, most ATMPs that achieved a positive reimbursement decision had a price agreement in place; uncertain/low quality clinical evidence and/or unsuitable pharmacoeconomic models were common critiques of submissions by appraising agencies.

Conclusions

- In European countries with a typical level of pharmaceutical spending, patient access to ATMPs is often limited.
- Most ATMPs with a positive recommendation achieved regular reimbursement following a successful price negotiation.
- Notably, a positive recommendation was often achieved despite low quality or uncertain clinical and economic evidence if a financial agreement was successfully negotiated.
- Alternative funding processes and financial agreements for ATMPs can make the difference in such products being cost-effective and achieving reimbursement.

Abbreviations

ATMP = advanced therapy medicinal products; ADA-SCID = adenosine deaminase deficiency; ALL = acute lymphoblastic leukaemia; DLBCL = diffuse large B-cell lymphoma; EU= European Union; MA = marketing authorisation; ND = no data; NR = not reported.

References

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Table 1. Outcomes of ATMP HTA by country

Product (date of MA, ↑)	Indication (s)	Austria	Belgium	Czechia	Luxembourg	Netherlands	Poland	Portugal	Sweden
HEMGENIX® (Feb 2023)	Haemophilia B	–	–	–	–	–	–	–	–
ROCTAVIAN® (Aug 2022)	Haemophilia A	–	–	–	–	–	–	–	–
CARVYKTI® (May 2022)	Multiple myeloma	–	–	–	–	–	–	–	–
BREYANZI® (Apr 2022)	B-cell and follicular lymphoma	–	–	–	–	–	–	–	–
TECARTUS® (Dec 2021)	Mantle cell lymphoma	–	–	✓	–	–	–	–	✓
ABECMA® (Aug 2021)	Multiple Myeloma	–	–	–	–	–	–	–	–
LIBMELDY® (Dec 2021)	Metachromatic leukodystrophy	–	–	–	–	–	–	–	✓
ZOLGENSMA® (May 2020)	Spinal muscular atrophy	–	✓	✓	–	✓	–	✓	✓
LUXTURNA® (Nov 2018)	Inherited retinal dystrophy	–	–	–	–	✓	–	–	✓
YESCARTA® (Aug 2018)	B-cell lymphoma	✓	✓	✓	–	–	–	✓	✓
KYMRIAH® (Aug 2018)	B-cell acute lymphoblastic leukaemia (ALL)	✓	✓*	✓*	–	✓	–	✓	✓
	Diffuse large B-cell lymphoma (DLBCL)	–	✓*	✓*	–	✓**	–	✓	–
ALOFISEL® (Mar 2018)	Crohn's disease (complex fistulas)	–	–	–	–	✓	–	✓	–
SPHEROX® (July 2017)	Knee cartilage replacement	–	–	–	–	✓	–	–	–
STRIMVELIS® (May 2016)	Adenosine deaminase deficiency (ADA-SCID)	–	–	–	–	–	–	–	–
IMLYGIC® (Dec 2015)	Melanoma	–	–	–	–	–	–	–	–
HOLOCLAR® (Feb 2015)	Limbal stem-cell deficiency	–	–	–	–	–	–	–	–
Mean time to reimbursement decision from MA (months):		**26**	**20**	**17**	**ND**	**26**	**18**	**26**	**23**

✓ Positive reimbursement recommendation – Negative reimbursement recommendation – Not reported or pending assessment

**Both indications considered under the same appraisal; **Received an initial negative reimbursement decision.*

Table 2. KYMRIAH® (Diffuse large B-cell lymphoma indication), HTA outcome summary by country

Country	Belgium	Czechia	Netherlands	Portugal	Sweden
Condition severity	- NR	↑ High	↑ High	↑ High	↑ High
Clinical appraisal decision	Added value	- NR	Added value	Added value	- NR
Type of clinical evidence submitted	Indirect comparison	- NR	Indirect comparison	Indirect comparison	Clinical Study
Type of managed entry agreement	Outcomes-based	- NR	Financial	Outcomes-based	- NR
Price agreement	Yes	- NR	Yes	Yes	Yes
Final decision	✓ Reimbursed	✓ Reimbursed	✓ Reimbursed	✓ Reimbursed	– Not reimbursed

ISPOR Europe 2023