HTA44

Reimbursement Outcomes for EMA Conditionally Authorized Orphan Drugs (2022-2023): Implications for Joint Clinical Assessment Requirements

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Introduction & Objectives

Current evidence requirements for orphan drugs (ODs) with conditional marketing authorization (CMA) vary across European HTA bodies. With mandatory Joint Clinical Assessment (JCA) implementation in 2025 introducing unified evidence standards, understanding how ODs with recent CMA perform against national HTA requirements should help to identify potential systemic challenges.

Key Objectives:
- Analyze HTA outcomes for CMA ODs (2022-2023)
- Identify critical evidence gaps against JCA criteria
- Provide guidance for manufacturers on potential evidence requirements

Methods

We conducted a systematic analysis of HTAs for 17 ODs with CMA (9 in 2022, 8 in 2023). Data was extracted from official HTA body websites.

Assessment outcomes were categorized as:
- Positive (reimbursed)
- Restricted
- Negative (insufficient benefit)

Key JCA requirements considered:
- Non-RCT risk of bias evaluation
- Surrogate outcome validation
- Network evidence assessment
- Methodology for non-randomized comparisons

JCA Criteria in HTA Decisions

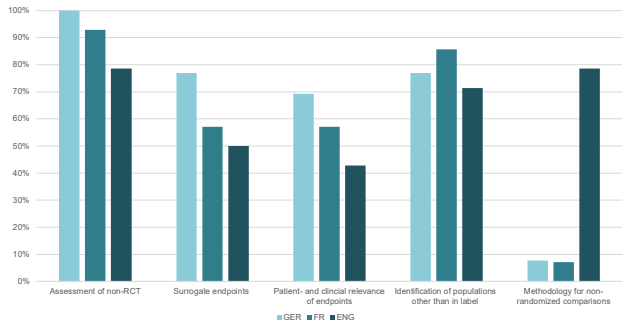

***Figure 1**: Frequency of JCA criteria mentions in HTA rationales (2022-2023)*

***Note**: While England is no longer part of the EU and thus not subject to JCA, it was included in this analysis as a methodological reference point due to its comprehensive HTA approach and transparent assessment criteria, providing valuable insights for comparison with EU member states.*

Results

There were consistent patterns across HTA bodies, with negative or restricted recommendations driven by evidence limitations that would also be critical under JCA requirements:
- Lack of RCTs (76%)
- Insufficient comparative data (82%)
- Inadequate follow-up periods (56%)

2022 approvals (n=9): Evidence limitations led NICE to issue positive recommendations for only 5 products (56%). All required managed access or commercial arrangements to address evidence gaps.
HAS led to grant insufficient ratings in 22% of cases or receive no dossier submission, while G-BA could not quantify additional benefit in 44% of cases due to methodological limitations that align with proposed JCA criteria.

HTA Rationale Analysis (2022)

***Table 1**: Selected national HTA rationale (Germany, France, England) in assessments along JCA requirements in 2022*

JCA evidence requirements	Comparative RCT	Patient relevance of endpoints	No or validated surrogate endpoint	Match of population PICO and against label	Methodology for non-randomised comparisons
Mentionings in HTA evaluation	Assessment Non-RCT	Lack of patient relevant endpoints	Presence of surrogate endpoint	Discrepancy population (label/trial or other selected population)	Uncertain/not valid ITC *(valid ITC not displayed)*
Carvykti	FR	DE	DE, +	DE, FR, +	
Hemgenix	FR, +	DE	DE, FR, +	DE, FR	
Lunsumio		DE	DE, FR, +	DE, FR, +	
Paxlovid	DE			DE, FR, +	
Roctavian	FR			DE	DE
Spevigo	FR, DE			DE, FR	
Tecvayli	FR	DE		FR, +	Valid, +
Zynlonta	Limited Comparison, +			DE, +	

HTA Rationale Analysis (2023)

***Table 2:** Selected national HTA rationale (Germany, France, England) in assessments along JCA requirements in 2023*

JCA evidence requirements	Comparative RCT	Patient relevance of endpoints	No or validated surrogate endpoint	Match of population PICO and against label	Methodology for non-randomised comparisons
Mentions in HTA evaluation	Assessment Non-RCT	Lack of patient relevant endpoints	Presence of surrogate endpoint	Discrepancy population (label/trial or other selected population)	Uncertain/not valid ITC *(valid ITC not displayed)*
Columvi	FR, +	DE	DE	DE, FR	
Elrexfio	DE, FR, +			DE, FR, +	FR, DE, +
Lytgobi	FR, +			FR	DE, +
Talvey	FR				
Tepkinly	DE, FR, +	DE		FR, +	+
Casgevy	FR, +			FR, +	+

Evidence Ambition Matrix for CMA Products

Stage: PH IIB / III Stage: PH II / pre-pivotal

Core evidence
Evidence priority: Validity of clinical studies (RCT) + patient clinical relevant endpoints
Other: Early Access program planning
Early mitigation: Method for non-randomised comparison

Adjacent evidence
Evidence priority: Population, pre-treatments, treatment pathways clinical relevant endpoints
Other: Early Access program implementation
Early mitigation: PICO feasibility

Transformational evidence
Evidence priority: Align value substantiating evidence to value proposition across/per markets
Other: Patient /carer organisation collaboration
Early mitigation: Satisfying a health service/patient need; level of change of current treatment pathway

Key Implications:
- Start planning for PICO in parallel to pivotal protocol and connect to patient/clinical relevance of endpoints
- Mitigation (such as ITC) is an ongoing process starting pre-pivotal
- Determine early the evidence pathway of patient population differentiation/pathways/pre-treatments

Conclusions

Our analysis demonstrates that orphan CMA drugs submitted with high uncertainty evidence (Phase I/II trials) fail to meet current HTA requirements, leading to restricted recommendations or additional evidence demands. This poses a significant challenge for the upcoming JCA implementation.
The evaluation of 17 orphan drugs with CMA shows consistent evidence limitations across HTA bodies, including lack of comparative RCT data (76%), insufficient comparisons (82%), and inadequate follow-up periods (56%). JCA implementation is likely to amplify these challenges due to its emphasis on comparative effectiveness.
Major variations were observed between countries in how HTA bodies evaluate indirect treatment comparisons and define patient-relevant endpoints. Germany applies more stringent criteria for surrogate endpoints, while all countries raise concerns about population discrepancies.
A phased evidence planning approach is recommended, beginning in Phase II with alignment on methodology for non-randomized comparisons. This holistic approach considering both regulatory and HTA requirements from early development phases will facilitate access to innovative orphan drugs while ensuring robust evidence generation.

Acknowledgements:
This research was presented at the EPA World Congress 2025

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ISPOR 2025: 2025-RS-5971-ISPOR