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Evolution of Health Technology Assessment for Rare Diseases and its Impact on Access

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Code: HTA30

Objectives

Identify and assess adaptations made by HTA for rare diseases

- Drug development and Health Technology Assessment (HTA) of rare diseases are subject to challenges related to clinical and economic evidence generation. HTA agencies have had to adjust their existing practices to overcome these unique challenges, which include: exceedingly small patient populations, limited data availability, and the need for non-traditional clinical trial designs and endpoints
- This study identified and assessed the adaptations made by different HTA processes to accommodate the assessment of treatments for rare diseases and their evolution over time

Methods

- A qualitative analysis of HTA reports and FDA/EMA responses to regulatory submissions for rare diseases treatments in the UK, France, Germany, Italy, and the US between 2018 and 2023 was performed
- Reports were analysed to assess the sources of uncertainty mentioned, comparators, trial design and the impact of each variable on reimbursement status and time to reimbursement

Challenges for HTA

Rare diseases present unique challenges for HTA bodies due to:

- **Limited data:** very small patient populations result in smaller and fewer clinical trials
- **Heterogenicity of some rare diseases:** it is difficult to generalise clinical evidence or identify sub-populations
- **Difficulty in identifying appropriate endpoints:** often rare diseases are evaluated based on surrogate endpoints rather than traditional mortality or morbidity endpoints
- **Ethical considerations**, particularly for treatments for life-limiting or severely debilitating conditions
- **High drug development costs:** they lead to higher expected prices for these therapies

Results

	Molecule	Sources of uncertainty	RWE use	Assessment outcome
Germany	Takhzyro® (Lanadelumab-Flyo)	• Discontinuation of long-term prophylaxis excluded or did not receive current standard of care	• Registries to retrieve clinical trial data and efficacy data in the study pool	• Considerable additional benefit
	Luxturna® (Voretigene neparvovec)	• Uncertain long-term efficacy • Use of subjective metrics	• Undertake a long-term study to assess both efficacy and safety	• Quantifiable additional benefit
	Zolgensma® (Onasemnogene abeparvovec)	• Long-term safety due to limited follow-up • Efficacy maintenance • Absence of data on cognitive development and QoL	• Mandated RWE collection to due limited clinical data	• Non-quantifiable added benefit
	Libmeldy® (Autologous autotemcel)	• Maintenance of efficacy in the long-term • Safety	• NHS used as supporting evidence	• Major additional benefit
	Kymriah® (Tisagenlecleucel)	• Lack of long-term safety data, • Maintenance of long-term clinical efficacy	• Registry data was deemed insufficient due to differing population	• Non-quantifiable added benefit
France	Takhzyro® (Lanadelumab-Flyo)	• No direct comparison with standard of care to allow prioritisation. Evaluation based on methodologically limited non-comparative open-label phase III (SPRING) trial	• Post-ATU observational study (SERENITI) in France has been finalized	• Recommended via early access authorisation • SMR: Substantial; ASMR: III
	Luxturna® (Voretigene neparvovec)	• Treatment initiation requires a multidisciplinary consultationLack of QoL data		• Recommended • SMR: Substantial; ASMR: II
	Zolgensma® (Onasemnogene abeparvovec)	• Medium and long-term safety due to limited follow-up, Real-world efficacy in patients older than 6 weeks, Efficacy maintenance and Absence of data on cognitive development and QoL	• NHS used as supporting evidence	• Recommended with restriction • SMR: Substantial; ASMR:III
	Libmeldy® (Autologous autotemcel)	• Maintenance of efficacy in the medium and long term, Safety Impact on fertility	• NHS used as supporting evidence	• Reimbursed via early access authorization • SMR: moderate ; ASMR: III
	Kymriah® (Tisagenlecleucel)	• Lack of long-term safety data, Maintenance of long-term clinical efficacy, particularly in terms of achieving a cure for patients in long-term remission	• Additional RWE data to support conclusions	• Recommended • SMR: Important ; ASMR: IV
Italy	Takhzyro® (Lanadelumab-Flyo)	• Efficacy data limited to short observation period. Safety profile requires further development for safety concerns. Therapeutic advantage not well-defined. Quality of trial evidence only moderate.	• Efficacy demonstrated on non-clinical outcomes used as supporting evidence	• Recommended
	Luxturna® (Voretigene neparvovec)	• AIFA registry mandatory to select eligible patients and to monitor treatment response		• Reimbursed with restriction
	Zolgensma® (Onasemnogene abeparvovec)	• Fatal cases of liver failure have been reported and liver function should be monitored closely	• NHS used as supporting evidence	• Reimbursed with restriction
	Libmeldy® (Autologous autotemcel)	• Maintenance of efficacy in the long term	• NHS used as supporting evidence	• Recommended
	Kymriah® (Tisagenlecleucel)	• Eligible patients and to monitor treatment response for the management of risk-sharing agreement (payment at result)	• Observational study to support treatment response	• Reimbursed with restriction
UK	Takhzyro® (Lanadelumab-Flyo)	• Cost-effectiveness uncertain Does not meet NICE criteria for life-extending treatment at end of life. Lower dosing can be used, but no clinical trial evidence supporting this switch.	• Non-interventional observational study used to support clinical effectiveness and safety	• Recommended subject to a confidential commercial agreement
	Luxturna® (Voretigene neparvovec)	• Lack of long-term clinical data Economic model assumptions		• Recommended through HST pathway
	Zolgensma® (Onasemnogene abeparvovec)	• Medium and long-term safety due to limited follow-up, real-world efficacy in patients older than 6 weeks, efficacy maintenance and absence of data on cognitive development and QoL	• NHS used as supporting evidence	• Recommended with restricted population through HST pathway
	Libmeldy® (Autologous autotemcel)	• Uncertainties around long term efficacy • Economic model assumptions	• Long-term study to assess efficacy and safety	• Recommended through the HST pathway
	Kymriah® (Tisagenlecleucel)	• Unclear if there is a need for subsequent stem cell therapies Uncertainty in cost-effectiveness	• NHS used as supporting evidence	• Funded via CDF as part of MAA

Adaptations made by HTA bodies:

- G-BA has a specialised assessment processes for orphan conditions which have an expected total cost of <20 M EUR per year
- NICE, HAS, and AIFA have adjusted their economic model guidelines to allow a lifetime horizon for therapies with a long-term impact, with recommendations around discount rates
- NICE published updated processes in January 2022 to incorporate additional elements of value such as severity modifier, rarity, equity, unmet need, and innovation
- To expand data collection through registries, France has developed a national database for rare diseases (BNDMR)
- Italy has established multiple monitoring registries where data on products use are routinely collected
- RWE use hasbecome more frequent across submissions and in some cases a mandatory post approval obligation

Conclusion

- HTA bodies have developed and adjusted their pathways to meet the unique challenges presented by treatments for rare diseases and to ensure the objective evaluation of these therapies
- These evolutions will have a significant impact on cell and gene therapies, which are mostly developed for rare or orphan diseases
- Progress towards understanding the limitations of evidence generation for these new therapies has led to a better understanding of how HTA pathways can be adjusted to accommodate their specific requirements, as further developments and insights are gained further adjustments may be needed to facilitate innovation

Abbreviations:
AIFA, Agenzia Italiana del Farmaco; CDF, Cancer Drugs Fund; EMA, European Medicines Agency; FDA, Food and Drug Administration; G-BA, Gemeinsamer Bundesausschuss; HAS, Haute Autorité de Santé; HST, highly specialised technology; HTA, Health technology Assessment; MAA, managed access agreement; NHS, natural history studies; NICE, National Institute for Health and Care Excellence; QoL, quality of life; RWE, real-world evidence.

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