The key to success for estimating durability in cost-effectiveness-focused markets

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Objective

One-time or single-dose gene therapies (GTs) have had varying success convincing cost-effectiveness (CE)-focused markets of their long-term durability. In CE markets, there has not been a consistent approach to the assumptions made around durability within economic models

This research aims to understand how durability is assumed for GTs in economic models and what evidence is necessary to support these claims

Methods

The appraisals of three GTs by the Canadian Agency for Drugs and Technologies in Health (CADTH) (now Canada's Drug Agency) and the National Institute for Health and Care Excellence (NICE, England), were analysed to understand the methodology used to assess durability within the health technology assessments (HTAs). Results of these analogue analyses were validated using insights from primary research with former payers from CADTH (N=3) and NICE (N=3)

Gene therapy appraisals analysed[1-6]:

zolgensma® (onasemnogene abeparvovec-xioi) | LUXTURNA® voretigene neparvovec-rzyl for subretinal injection | HEMGENIX® etranacogene dezaparvovec-drlb

Results

Assumed years of durability

Drug	Durability assumed	
	CADTH	NICE
Zolgensma®	80 years	80 years
Luxturna®	10 years	40 years
Hemgenix®	Inconclusive	Inconclusive

Overview of evidence types considered by CADTH and NICE to support durability claim

Evidence considered to support durability claim	Zolgensma®		Luxturna®		Hemgenix®	
	CADTH	NICE	CADTH	NICE	CADTH	NICE
Randomized clinical trial (RCT)	-	-	-	-	-	-
Real-world evidence (RWE)	✓	✓	-	-	-	-
Long-term follow-up (LTFU)*	✓	✓	✓	✓	-	-
Regression-based models	✓	✓	✓	✓	×	×
Analog data	×	×	-	-	-	✓
Clinical expert opinion	✓	✓	×	✓	✓	✓
Patient group input	×	×	×	×	✓	×
Biological plausibility	✓	✓	×	✓	✓	×

✓ Evidence supported durability claim × Evidence did not support durability claim - Evidence not included in the dossier

***Defined as ≥3 years, non-comparative follow-up**

Key Drivers of Durability

RWE & LTFU are key drivers for supporting long-term durability of gene therapies

CADTH and NICE valued the opinion of clinical experts to better estimate durability, both to the benefit or detriment of a gene therapy appraisal:

- Clinical expert's supported appraisals by explaining whether a long-term treatment effect is biologically plausible
- Clinical expert opinion was leveraged to validate regression-based models

Of the gene therapies analysed, Zolgensma® achieved the longest durability assumed at 80 years. This is due to totality of evidence available to support the manufacturer's durability claim, clinical expert opinion on biological plausibility, and critically, RWE, which neither Luxturna® or Hemgenix® had in their dossiers

Differences between CADTH & NICE

When evaluating Luxturna®, CADTH & NICE assumed 10 years and 40 years of durability, respectively

Differences in clinical expert opinion was a key factor for variations in long-term benefit. CADTH and NICE experts also drew on **biological plausibility arguments** to support or question long-term benefit assumptions used in CE modelling:

- CADTH clinical experts expected the treatment effect of Luxturna® to wane over time
- NICE clinical experts explained that a long-term treatment effect with Luxturna® is biologically plausible and is their expectation

Primary research insights

In Canada and England, apart from RCT data, clinical expert input would likely have the most impact as experts would be asked to comment on plausibility of assumptions by the manufacturer

There is a greater willingness to accept lower levels of evidence (i.e., clinical expert opinion) for therapies which address pediatric or younger patient populations in rare diseases

Payers from Canada highlighted that RWE and LTFU are becoming increasingly important to mitigate uncertainties with clinical trial data

Payers from England valued regression-based modelling very highly, along with RWE and LTFU

Conclusion

When developing economic models in Canada and England, durability of a GT is informed primarily by clinical data and supplemented by lower, yet still important, levels of evidence. Manufacturers can optimise appraisal outcomes of GTs in these two markets by providing a robust data package with adequate patient numbers (relative to the disease), sufficient long-term follow-up, and support from clinical experts on the biological rationale for durability of the therapy

Clinical expert opinion

This research has revealed that in the research CE markets, clinical expert opinion plays a major role in advising HTAs on biological plausibility and the likelihood that the benefit of a one-time therapy will be maintained over time. However, the opinion of clinical experts on the durability of a GT could differ, such as with Luxturna®, and therefore a national/local approach to clinician engagement is necessary

Expectations for durability

Payers expect manufactures to provide their own definition of durable treatment effects for a given therapy. As CE markets, Canada and England will model treatment effect over a lifetime horizon. Durability expectations are influenced by negotiated price, budget impact, severity of disease and level of unmet need

Sources: *1. Zolgensma® CADTH Canadian Drug Expert Committee Recommendation (March 26, 2021); 2. Zolgensma® NICE guidance (April 19, 2023); 3. Luxturna® CADTH Canadian Drug Expert Committee Recommendation (November, 2020); 4. Luxturna® NICE guidance (October 9, 2019); 5. Hemgenix® CADTH Canadian Drug Expert Committee Recommendation (May, 2024); 6. Hemgenix® NICE guidance (July 24, 2024).*