The Hidden Cost of Access: Integrating HTA, Evidence Generation, and Managed Entry Agreement Requirements into Cost-Based Pricing Models for Cell and Gene Therapies

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Introduction

Background

Cell and gene therapies (CGTs) are frequently criticised for high prices, with list prices often above €1 million per patient. Cost-based pricing models focus on R&D, manufacturing and regulatory expenditures. Costs after regulatory approval, including HTA requirements, evidence generation, long-term monitoring, pricing negotiations and managed entry agreements (MEAs), are not included (Figure 1).

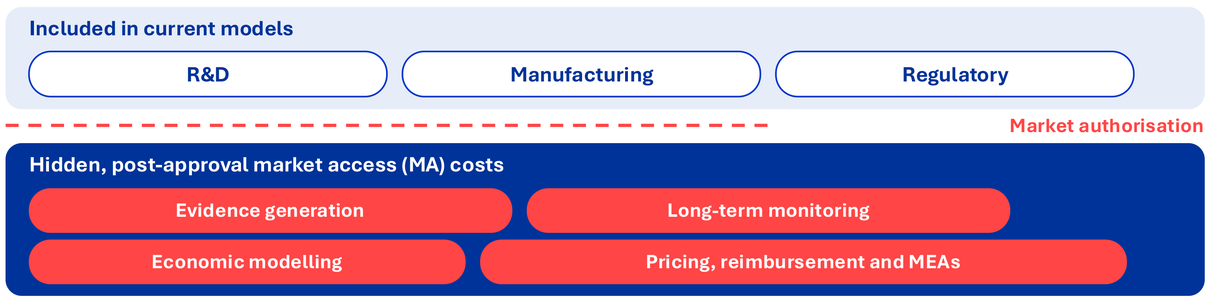


Figure 1. *Cost components in current cost-based pricing models vs hidden post-approval costs*

Objective

To identify and quantify these hidden MA costs, assess their impact on cost-based pricing estimates for CGTs, and compare how the Dutch (ZIN) and UK (NICE) HTA systems evaluated the same therapies.

Methods

A three-step mixed evidence approach was applied to three approved CGTs: Zolgensma (reimbursed in NL and UK), Abecma (UK only) and Carvykti (NL only).

1 Pragmatic literature review

Identified development, manufacturing, regulatory and MA costs using academic literature, annual reports, SEC filings, HTA reports and industry sources.

2 Qualitative document analysis

EMA, NICE and ZIN assessments were analysed to map post-approval requirements to manufacturer activities, deriving hidden cost categories such as long-term monitoring and pricing processes.

3 Extended cost-based pricing model

Risk-adjusted R&D costs, manufacturing costs, cost of capital and MA costs were integrated, with one-way and scenario sensitivity analyses to estimate per-patient price impacts (Figure 2).

$$Ctx = \{[(C_{R\&D} + C_{EM} + C_{EG} + C_{LTM} + C_{P\&R}) / N_p] + C_{man}\} \times (1 + M_p)$$

Extends Uyl-de Groot and Löwenberg (2018) with economic modelling (EM), evidence generation (EG), long-term monitoring (LTM), and pricing and reimbursement (P&R) costs, shown in coral. P&R could not be quantified and was retained qualitatively.

Figure 2. *Extended cost-based pricing model*

Results

HTA requirements

HTA evaluations imposed post-approval requirements, adding manufacturer activities (Figure 3):

- **Additional clinical studies**
- **Extended follow-up periods**
- **Revised cost-effectiveness models**
- **Comparative effectiveness analyses**
- **Outcome-based reimbursement**

Figure 3. *Post-approval requirements set by HTA bodies*

Hidden cost estimates

These costs are not reported as discrete items, so clinical trial cost benchmarks and company reports were used as proxies (Figure 4).

Evidence generation
USD 4.0 to 15.0 M
per trial

Long-term monitoring
USD 2.8 to 10.9 M
per trial

Economic modelling
2.7%
of total R&D expenditure

P&R negotiation
Not quantifiable
no published estimate

Figure 4. *Quantified hidden market access cost categories*

Per-patient price estimates

Incorporating hidden costs resulted in per-patient prices of €538,602 for Zolgensma, €148,778 for Abecma and €159,444 for Carvykti. All estimates remained well below list prices, even when preclinical R&D was added (Figure 5).

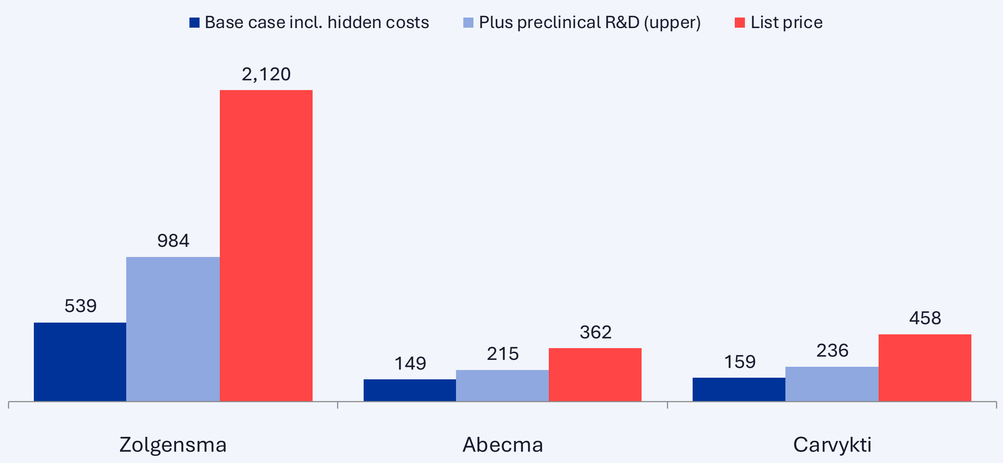


Figure 5. *Estimated per-patient price vs list price, EUR thousands*

+41.6%
Zolgensma price vs the prior cost-based price excluding MA costs

37 to 59%
of list price, even with preclinical R&D costs added

ZIN vs NICE: same evidence, different decisions

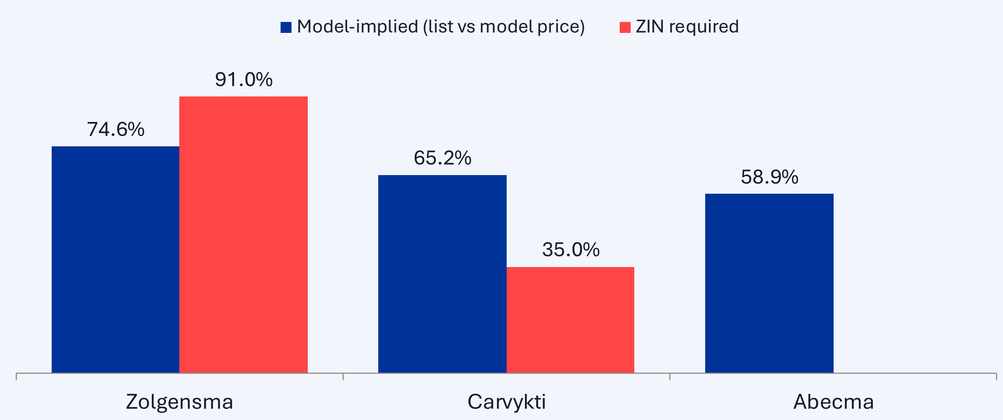
NICE emphasises explicit cost-effectiveness thresholds, while ZIN emphasises clinical benefit and negotiates price separately after its advice. As a result, the two agencies reached opposite decisions for Abecma and Carvykti (Figure 6).

	ZIN (Netherlands)	NICE (UK)
Zolgensma	**Conditional** Pay-for-performance MEA, 91% price cut required	**Recommended** HST threshold £100,000/QALY, with MEA
Abecma	**Not reimbursed** Insufficient added clinical benefit	**Accepted** Uncertainty managed through an MEA
Carvykti	**Pending price** 35% then a further 5% cut, still in the sluis	**Not recommended** Manufacturer withdrew from appraisal

Figure 6. *ZIN and NICE reimbursement decisions by therapy*

Model-implied vs ZIN-required discount

ZIN required a steeper cut than the cost-based model implies for Zolgensma, but a smaller one for Carvykti (Figure 7). Required discounts reflect the evidence at assessment, not only the gap between list price and cost.



Abecma: reimbursement declined, no discount set. Carvykti: initial 2025 advice.

Figure 7. *Model-implied vs ZIN-required price reduction*

Conclusions

- **Current pricing models may underestimate the total cost burden of CGTs by excluding post-approval MA requirements.**
- HTA-driven evidence generation, monitoring obligations and reimbursement processes may be important cost drivers in cost-based pricing analyses.
- Even with hidden costs included, estimated prices stayed well below list prices, and ZIN and NICE reached opposite decisions on the same evidence.
- Incorporating hidden costs may improve transparency and provide a realistic understanding of the economic challenges of CGT access.

Limitations

- Patient numbers were extrapolated from partial disclosures.
- Manufacturing costs were proxied by published gene therapy estimates.
- Preclinical R&D was excluded from the base case.
- Hidden costs rely on clinical trial benchmarks.

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