CLEVER ACCESS

HTA3

Anticipating the Value- and Price-Determination Challenge of GLP-1 RA Indication Expansion Across Heterogeneous Therapeutic Areas: Lessons from PD-1/PD-L1 and TNF-α Inhibitors Indication Expansion

Hend Jedidi[1], Aurélie Millier[2], Aleksandra Caban[3], Lylia Chachoua[2], Mondher Toumi[4]

1 Clever-Access, Tunis, Tunisia; 2 Clever-Access, Paris, France; 3 Clever-Access, Krakow, Poland; 4 Aix-Marseille University, Marseille, France

BACKGROUND

GLP-1 receptor agonists and related multi-agonists (GLP-1-based therapies) are expanding beyond type 2 diabetes (T2D) and obesity into cardiovascular, kidney and liver disease, and obstructive sleep apnoea (OSA); trials in Alzheimer's disease and alcohol use disorder are under way.[1-4] Differences in target **populations, comparators and outcomes** create challenges for demonstrating value to HTA bodies. This raises questions about how indication-specific value translates into **pricing throughout the product lifecycle**, including after loss of exclusivity (LoE).

PD-1/PD-L1 inhibitors and TNF-α inhibitors (adalimumab), as precedent examples of indication expansion within and across therapeutic areas,[5-8] offer insights into the interaction between value assessment, pricing and post-exclusivity competition.

OBJECTIVE

To anticipate the HTA, value and pricing challenges associated with GLP-1 indication expansion, using PD-1/PD-L1 inhibitors and adalimumab as precedents.

Particular focus: heterogeneity in evidence requirements, indication-specific value, and post-LoE competition.

METHODS

Targeted review of pembrolizumab, nivolumab and adalimumab HTA reports in France (HAS),[9] Germany (G-BA/IQWiG)[10] and England (NICE),[11] alongside published pricing evidence:

- **HTA review:** compared decisions by drug, indication and country, retaining country-specific recommendation categories.
- **Outcomes and value:** examined disease-specific endpoints and clinical benefit assessment versus QALY-based economic evaluation.
- **Pricing and LoE:** reviewed list prices, reported net prices/discounts and examined adalimumab competition following LoE.
- **The evolving GLP-1 evidence landscape:** reviewed approvals[12] and ClinicalTrials.gov records[4] and used example findings to identify potential implications for GLP-1 evidence and pricing strategy.

RESULTS

1. VALUE IS INDICATION-SPECIFIC • same drug, different indications, endpoints and HTA outcomes

Among reports reviewed, indications were assessed separately; no rating was carried over from one indication to the next. ASMR III was most frequent (21/27) in **HAS opinions**.[9] Even the same drug in the same indication was rated differently by subgroup in the **binding G-BA resolution**. For example, nivolumab/ipilimumab received considerable added benefit in non-epithelioid mesothelioma, but added benefit was not proven in epithelioid disease.[10]

Of 25 NICE indications, 18 received routine recommendations, 6 Cancer Drugs Fund recommendations pending mature survival data, and 1 was rejected.[11]

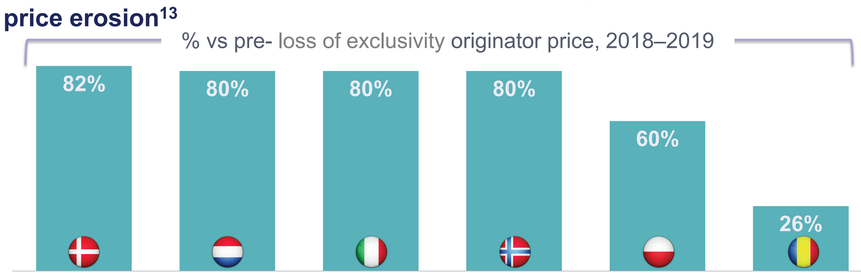
2. EVIDENCE NEEDS WILL MULTIPLY • GLP-1 indications span hard, surrogate and clinical outcomes

Adalimumab and GLP-1-based therapies used disease-specific outcomes, limiting direct clinical comparison (**Table 1**). QALY-based evaluation provided a common economic metric while retaining indication-specific decision contexts.[4,9,10,11]

3. COMPETITION WILL RESHAPE PRICING • new indications may launch alongside older GLP-1-based therapies approaching or reaching LoE

Published pricing examples showed limited list-price variation during indication expansion, alongside discounts and price–volume agreements. Adalimumab experienced substantial reported net-price erosion following European biosimilar entry in 2018 (**Figure 1**).

Figure 1. Adalimumab illustrates the potential magnitude of post-LoE price erosion[13]



Netherlands: 80–90% (lower bound shown). Germany: list price largely unchanged; discounts off-list.

Table 1. Primary endpoint by indication and drug class[4,9,10,11]

Drug class	Indication area	Primary endpoint	Type
PD-1/PD-L1	Multiple tumour types	OS PFS	Hard clinical outcome Surrogate
Adalimumab	Rheumatology (RA, PsA, AS)	ACR response, DAS28*; ASAS, BASDAI	COA (composite)*
	Dermatology (psoriasis, HS)	PASI; HiSCR	COA (ClinRO)
	Gastroenterology (CD, UC)	CDAI; Mayo score*	COA (composite)*
	Ophthalmology (uveitis)	Time to treatment failure	Clinical outcome
GLP-1-based therapies	Type 2 diabetes	HbA1c	Surrogate (biomarker)
	Obesity	Body-weight change†	Surrogate†
	Cardiovascular disease	MACE	Hard clinical outcome
	Chronic kidney disease	Kidney composite (FLOW) UACR	Hard clinical outcome Surrogate (biomarker)
	MASH	Liver histology; MRI-PDFF	Surrogate (biomarker)
	Obstructive sleep apnoea	Apnoea–hypopnoea index	Surrogate (physiological)
	Osteoarthritis, back pain	WOMAC, NRS pain	COA (PRO)
	Alzheimer's disease	CDR-SB (EVOKE: not met)	COA (ClinRO)
	Alcohol use disorder	Heavy-drinking days	COA (PRO)

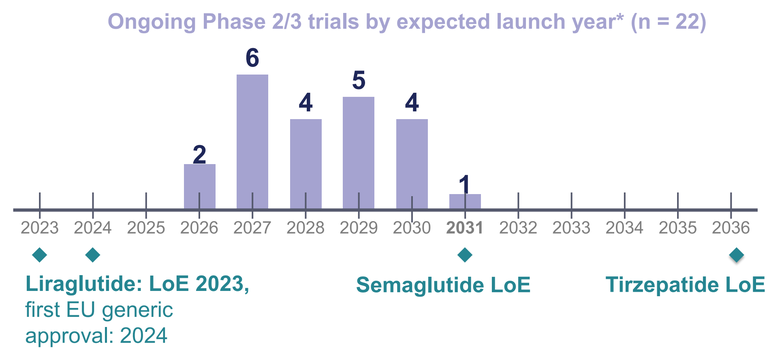
*ClinRO/PRO elements. †Regulatory efficacy endpoint; surrogate for HTA bodies. Biomarker/surrogate refers to an intermediate laboratory, imaging, physiological, histological or anthropometric measure used to predict a clinical outcome; surrogate status depends on the clinical context and strength of validation evidence[14,15]. **Abbreviations: COA:** clinical outcome assessment (classified as patient-reported, clinician-reported, observer-reported, or performance-based)[16]; **ClinRO:** clinician-reported; **PRO:** patient-reported; surrogate, **OS/PFS:** overall/progression-free survival; **ACR:** American College of Rheumatology response criteria; **DAS28:** Disease Activity Score in 28 joints; **ASAS:** Assessment of SpondyloArthritis International Society response criteria; **BASDAI:** Bath Ankylosing Spondylitis Disease Activity Index; **PASI:** Psoriasis Area and Severity Index; **HiSCR:** Hidradenitis Suppurativa Clinical Response; **CDAI:** Crohn's Disease Activity Index; **HbA1c:** glycated haemoglobin; **MACE:** major adverse cardiovascular events; **UACR:** Urine albumin-to-creatinine ratio; **MASH:** metabolic dysfunction-associated steatohepatitis; **MRI-PDFF:** magnetic resonance imaging–estimated proton density fat fraction; **AHI:** apnoea-hypopnoea index; **WOMAC:** Western Ontario and McMaster Universities Osteoarthritis Index; **NRS:** Numeric Rating Scale; **CDR-SB:** Clinical Dementia Rating–Sum of Boxes.

4. LAUNCHES WILL CLUSTER • many GLP-1 trial milestones within a short window

The scan identified at least nine distinct outcomes (**Table 1**).[4] These outcomes span clinical events, symptom and functional measures, and biomarkers, with differing implications for demonstrating patient-relevant benefit.

Among 23 ongoing Phase 2/3 trials, 4 assessed cardiovascular or kidney events (hard), 20 were placebo-controlled and none compared against another GLP-1-based therapy. More than 10 next-generation agents were in Phase 2/3 or under regulatory review, with up to 22 anticipated launches during 2026–2031.[4,12] **Figure 2** places these milestones alongside selected patent expiries.

Figure 2. GLP-1 indication expansion will coincide with an evolving LoE landscape



SYNCHRONIZE-2 trial excluded (no launch estimate). *Launch year: completion date + approximately 2 years.
4/23 event-based; 20/23 placebo-controlled; 0/23 GLP-1 comparisons

Abbreviations: LoE: loss of exclusivity; **EU:** European.

CONCLUSIONS

Value will need to be demonstrated indication by indication

Shared outcomes do not imply shared value. Differences in endpoints and reliance on surrogates may complicate HTA across GLP-1 indications.

Evidence strategy and pricing strategy will become increasingly interdependent

As GLP-1 indications expand and older agents approach LoE, evidence generation will need to anticipate both cross-indication value and increasing competitive pricing pressure.

After patent loss, a cheaper older GLP-1 could replace a newer agent where disease-specific evidence supports comparable effectiveness and safety (as illustrated by the publicly funded head-to-head trial of bevacizumab/ranibizumab).

Historical examples illustrate potential challenges but are not intended to predict future HTA decisions or price erosion.

GLP-1 indication expansion requires a portfolio-level approach to evidence generation, value demonstration and pricing strategy

01 Build the value story by indication

Plan populations, subgroups and comparators for each HTA decision. An earlier rating will not carry over.

02 Demonstrate meaningful patient benefit

Establish outcome relevance (validate surrogates where needed) & credible estimates of long-term benefit and QALYs.

03 Anticipate evolving competition

Assess relevant lower-cost comparators and the evidence needed for differentiation.

04 Align evidence generation with pricing strategy

Coordinate comparative evidence, indication milestones and pricing scenarios.

REFERENCES

1. Nauck MA, et al. Lancet. 2026;407:892–908.
2. Zarei M, Hajiani Y. Diabetol Metab Syndr. 2026;18:173.
3. Moiz A, et al. EClinicalMedicine. 2025;86:103363.
4. ClinicalTrials.gov
5. Samperio VM, et al. Expert Opin Biol Ther. 2026;26(8):837–856.
6. Chang E, et al. Oncologist. 2021;26(10):e1786–e1799.
7. Car E, et al. Front Pharmacol. 2023;14:1151764.
8. Lis K, et al. Arch Med Sci. 2014;10(6):1175–1185.
9. HAS website
10. G-BA website
11. NICE website
12. EMA website
13. Moorkens E, et al. Front Pharmacol. 2021;11:591134.
14. Grigore B, et al. Pharmacoeconomics. 2020;38(10):1055–1070.
15. Biomarkers Definitions Working Group. Clin Pharmacol Ther. 2001;69(3):89–95.
16. Walton MK, Powers JH III, Hobart J, et al. Value Health. 2015;18:741–52.
17. CATT Research Group, Martin DF, et al. N Engl J Med. 2011;364(20):1897–1908.
18. Chakravarthy U, et al. Lancet. 2013;382(9900):1258–1267.

Scan the QR code or email us to arrange a meeting.

Contact information: contact@clever-access.com