GLP-1 and SGLT2 Landscape:

Approvals, Evidence, and Market Positioning Insights

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BACKGROUND

- Type 2 diabetes (T2DM) is rising globally and creates a major clinical and economic burden. Newer diabetes medicines—especially SGLT2 inhibitors and GLP-1 receptor agonists—are now widely used because they offer benefits beyond glucose control, including cardiovascular and kidney protection.
- Jardiance (empagliflozin), an SGLT2 inhibitor, has strong evidence for reducing heart failure, cardiovascular events, and kidney disease risk. However, competitors like injectable semaglutide, oral semaglutide, and tirzepatide claim superior glucose-lowering, weight loss, and cost-effectiveness benefits.
- These claims are used in payer and HTA submissions across several countries. HTA agencies in the UK, Canada, Germany, France, Australia, and the US have reviewed these competitor products, with mixed outcomes—some approvals with restrictions and several negative decisions. Concerns include reliance on surrogate endpoints, lack of long-term outcomes, modelling uncertainty, and mismatched comparators.
- A combined review of payer objections, economic evidence, global HTA decisions, and modelling practices shows that competitor evidence often has limitations, while **Jardiance** maintains a **strong value story supported by real-world data and cardio-renal benefits.**

Pharmacological Action of Empagliflozin

➢ **What is Empagliflozin?**

Empagliflozin is an oral sodium–glucose co-transporter-2 (SGLT2) inhibitor used primarily for:

- Type 2 Diabetes Mellitus (T2DM)
- Heart failure (HFrEF & HFpEF), and
- Chronic kidney disease (CKD)

It was developed by **Boehringer Ingelheim**, in collaboration with **Eli Lilly**, and is marketed mainly under the brand **Jardiance®** and fixed-dose combinations.

- **Mechanism of action**

Selectively inhibits SGLT2 in the proximal renal tubules, reduces glucose reabsorption, and increases urinary glucose excretion.

- **Indications beyond diabetes**

It is approved not only for Type 2 Diabetes Mellitus (T2DM) but also for heart failure and chronic kidney disease (CKD) due to strong outcome trial evidence (EMPA-REG, EMPEROR, EMPA-KIDNEY).

- **Route of administration**

Oral only (tablets). No IV formulation is approved or marketed; all clinical and commercial forms are oral.

- **Cardiovascular mortality benefit**

First antidiabetic drug to show significant reduction in CV death in T2DM patients with established CV disease.

- **Low hypoglycemia risk**

Insulin-independent mechanism and low hypoglycemia risk unless combined with insulin or sulfonylureas.

Functionality of SGLT2 and GLP Medications

SGLT2 inhibitors like **empagliflozin (Jardiance)** work by helping the kidneys remove extra sugar from the body through urine.
This not only lowers blood sugar but also provides strong heart and kidney protection, which has been proven in major trials and real-world studies such as EMPA-REG and EMPRISE.
These medicines reduce risks of heart failure, cardiovascular death, and kidney disease, making them especially valuable for patients with cardio-renal risks.

GLP-1 receptor agonists like **semaglutide** (oral or injectable) work differently — they act like a natural hormone that increases insulin when needed, slows digestion, and reduces appetite.
This leads to greater HbA1c reduction and more weight loss compared to SGLT2 inhibitors.
However, HTA agencies often point out that much of the evidence for GLP-1 drugs is based on short-term or **surrogate outcomes** (like HbA1c and weight), with uncertain long-term cardiovascular benefit and modelling limitations.

Differences Between SGLT-2 Inhibitors and GLP-1 Medications

SGLT2	GLP1
They lower blood sugar by helping the kidneys remove excess glucose through urine.	They act like a natural hormone that increases insulin, slows digestion, and reduces appetite.
They have proven cardiovascular and renal benefits, including reduced heart failure, CV death, and kidney disease progression	Trials like PIONEER showed greater HbA1c and weight loss, but these are surrogate outcomes, not long-term clinical benefits.
Large real-world studies (like EMPRISE) showed empagliflozin reduced HF hospitalizations, major CV events, kidney problems, and mortality versus GLP-1 RAs	PIONEER-6 did not show major cardiovascular benefits, and many GLP-1 studies lacked mortality, QoL, or long-term complication data.
Studies from the US and Germany show patients on empagliflozin have lower total healthcare costs due to fewer hospital stays and lower medication costs.	Many semaglutides cost-effectiveness models rely on short-term data, unblinded trials, mixed populations, or high uncertainty.
HTA reviews consistently support SGLT2 inhibitors because they have robust long-term outcomes and fewer evidence uncertainties.	Health agencies (HAS, G-BA, PBAC) frequently issued negative or restricted decisions, citing modelling issues and lack of long-term evidence.

FDA History & Regulatory Milestones

Year	FDA Approval Update
2014	FDA approved Jardiance® (empagliflozin) for Type 2 Diabetes
2016	Reduction of cardiovascular death in T2DM with established CVD
2021	Heart failure with reduced ejection fraction (HFrEF)
2022	Heart failure regardless of ejection fraction (HFpEF & HFrEF)
2023	Chronic Kidney Disease (CKD)
2023	Pediatric T2DM (≥10 years)

Therefore, Empagliflozin became the first oral antidiabetic drug with strong CV and renal outcome claims.

ECONOMIC MODELLING

- **Models used**

Mostly IQVIA CORE Diabetes Model, plus Cardiff, IHE-DCM, UKPDS-OM, COMT, ECHO-T2DM. These simulate patient outcomes over decades using trial data and risk equations.

- **How was the modelling done?**

Models used clinical trial results to estimate how HbA1c/weight/BP changes affect long-term complications. They applied UKPDS 68/82 risk equations, which are older and may not match modern practice. Many models assumed treatment switch after 3–5 years, which is often unrealistic.

- **What the review found?**

SGLT2 vs GLP-1 cost-effectiveness results were mixed — **no clear winner**. Outcomes changed depending on modelling assumptions (risk equations, time horizon, switch rules). Industry-funded studies almost always favored the sponsor's own product.

- **Main problems with the models-**

✓ Outdated risk equations
✓ Unrealistic treatment pathways
✓ Heavy reliance on clinical trial data, not real-world data
✓ Inconsistent comparator choices
✓ Sponsor bias common

- **Conclusion -** Because modelling assumptions varied so much, you cannot reliably determine which drug class (SGLT2 or GLP-1) is truly more cost-effective. Better, more transparent, real-world-aligned models are needed.

RATIONALE AND RESULTS OF THE TLR

Type 2 diabetes is increasing very quickly worldwide.

- 536 million adults had it in 2021.
- Expected to reach 783 million by 2045.

Diabetes is extremely expensive for health systems.

- Costs grew from USD 232 billion (2007) to USD 966 billion (2021).Expected to cross USD 1 trillion by 2045.

There are old and new types of diabetes medicines.

- Older: Metformin, sulfonylureas
- Newer: SGLT2 inhibitors, GLP-1 RAs, DPP-4 inhibitors

Newer drugs have extra health benefits.

- Protect the heart
- Protect kidneys
- Help with weight loss
- Because of this, 2022 ADA guidelines suggest using SGLT2 inhibitors or GLP-1 RAs early, even before metformin in high-risk patients.

These newer medicines are costly, so their use is still limited.

- Boehringer Ingelheim asked IQVIA to study how HTA bodies compare and reimburse these drugs, and how competitors position their products.

RATIONALE AND RESULTS OF THE TLR

Economic studies showed mixed cost-effectiveness results and 12 economic evaluation studies were reviewed (mostly from the USA & UK) by using cost-effectiveness models.

- 5 studies → SGLT2 inhibitors more cost-effective
- 5 studies → GLP-1 RAs more cost-effective
- 2 studies → No clear winner

Competitors (semaglutide injectable, semaglutide oral, tirzepatide) generally focused on six key claims:

1. Stronger clinical effectiveness- Competitors claimed their products offer better overall clinical outcomes compared with empagliflozin.

2. Better glycemic control (HbA1c reduction)- They highlighted bigger drops in HbA1c than what empagliflozin achieves.

3. Superior weight loss benefits- Semaglutide and tirzepatide especially claimed greater weight loss vs SGLT2 inhibitors.

4. Better cost-effectiveness- Some competitors argued that, despite higher prices, their drug delivers more health benefit per cost than empagliflozin.

5. Injectable semaglutide- It promotes better glycemic control and greater weight loss

6. Oral semaglutide & tirzepatide- It ensures stronger clinical outcomes, weight loss, better HbA1c reductions, and cost-effectiveness claims

RATIONALE AND RESULTS OF THE TLR

HTA bodies(Canada, Germany, France, Australia, and the UK reviewed these drugs) found many weaknesses in these claims. They often rejected or criticized the claims because:

1. Long-term outcomes are still uncertain- Many GLP-1/GIP-GLP-1 drugs, long-term cardiovascular or renal data is not available yet.

2. Heavy reliance on surrogate endpoints- Many claims were based on HbA1c or weight loss only, not real clinical outcomes such as heart attacks, strokes, and mortality.

3. Unrealistic economic models- Some models assumed perfect long-term durability or benefits lasting many years—HTAs rejected these as too optimistic.

4. Weak trial comparators- In several trials, drugs were not compared against real-world standard treatments, making the results less convincing.

Therefore, **HTAs did not fully trust many of the competitor claims.**

Restrictions:

HTAs were often negative or restrictive for semaglutide because of uncertain long-term benefits, reliance on surrogate endpoints.

Tirzepatide looks promising but lacks long-term evidence- HTAs liked its strong weight loss and HbA1c results but they still refused full reimbursement because it does not yet have long-term cardiovascular outcome data.

What BI should highlight for Jardiance - It needs to target strong cardiovascular outcome evidence, renal protection, mature high-quality clinical data, and transparent and realistic economic modelling.

HTA REPORTS OF COUNTRIES

United Kingdom (NICE/SMC/NHSC) – The UK accepts GLP-1s and tirzepatide only with strict restrictions, mainly for later-line patients who have failed multiple therapies and meet BMI or clinical-need criteria; access is controlled and tightly rationed.

Canada (CADTH + INESSS) – Canada allows oral and injectable semaglutide with restrictions, but cost-effectiveness is a problem, especially in Quebec where INESSS considers oral semaglutide not cost-effective vs SGLT2s, resulting in narrow, conditional funding.

Germany (G-BA + IQWiG) – Germany does not grant added benefit to semaglutide (oral or SC), meaning no premium pricing and limited uptake; GLP-1 benefits are considered non-patient-relevant due to reliance on surrogate endpoints like HbA1c.

France (HAS) – France only reimburses semaglutide SC in very specific dual/triple therapy combinations, while rejecting oral semaglutide and broader uses due to insufficient evidence and lack of clinical advantage.

Australia (PBAC) – Australia accepts semaglutide SC with restrictions but rejects tirzepatide entirely due to high ICERs and huge projected budget impact, making GLP-1/GIP therapies harder to access.

FDA & Obstacles

- **Approves new drugs and vaccines after checking safety, quality, and effectiveness.**
- **Regulates food safety, including additives and labeling.**
- **Monitors medical devices (from syringes to implants) for safety and performance.**
- **Ensures drug quality by inspecting manufacturing plants and enforcing GMP rules.**
- **Conducts post-marketing surveillance to track side effects and take action if risks appear.**

OBSTACLES:

➢ **Very strict approval requirements**

Even though the drug worked well, this slowed down its availability to patients.

➢ **Separate approval needed for each new use**

Patients had to wait years before the drug could officially be used for heart or kidney protection.

➢ **Safety warnings reduced early acceptance**

These warnings made many doctors hesitant to prescribe Empa, especially when it was new.

➢ **Long patent protection delayed generics**

Empa remained very expensive for many years in the US, limiting patient access.

➢ **FDA approval works only in the US**

This caused delays in worldwide rollout, even when the drug was already proven effective.

OBJECTIONS

- There is no strong evidence that **injectable semaglutide is better than empagliflozin.**
- Semaglutide cannot be proven more **cost-effective** because studies supporting it have weak methods, while real-world evidence favors empagliflozin.
- Evidence is too weak to claim semaglutide works better but empagliflozin shows stronger long-term heart and kidney benefits.
- Real-world cost outcomes favor empagliflozin; semaglutide’s cost-effectiveness claims are unreliable.
- Oral semaglutide lowers HbA1c more, but empagliflozin has proven cardiovascular and survival benefits that semaglutide does not.
- Long-term and real-world evidence shows **empagliflozin is more cost-effective** than oral semaglutide.
- Evidence suggesting tirzepatide is superior is weak but empagliflozin has proven real-world benefits, tirzepatide does not.
- Tirzepatide’s cost-effectiveness claim depends on unrealistic pricing and incomplete data; **empagliflozin has stronger long-term real-world economic value.**

LIMITATIONS

- **Short literature search period**

The review only searched within a limited timeframe; hence some relevant studies may have been missed.

- **Excluded non-DAM (Decision-Analytic Models) studies**

Only DAM-based economic evaluations were included. Other useful study types were ignored, which may have removed valuable information.

- **Review only compared nNIADs with other nNIADs**

Studies comparing new non-insulin drugs (nNIADs) vs older drugs (like metformin) were not included. This reduces understanding of full cost-effectiveness across all treatment options.

- **Excluded non-English papers**

Many Asian studies were likely missed because only English-language papers were reviewed.

- **Counted all published papers separately**

Some papers were adaptations of the same model in different settings, but the review treated them as separate studies which might overrepresent certain findings.

STRENGTHS

- **Broad extraction of model assumptions**

The study reviewed a wide range of model inputs and assumptions, giving deeper insight into how each economic model works.

- **Goes beyond basic economic outcomes**

Instead of just reporting ICERs or costs, the study looked at underlying methods and modeling choices, hence adding richer context.

- **Helps decision makers understand modeling variability**

Highlighting how different assumptions lead to different results makes it easier for policymakers to interpret cost-effectiveness evidence.

- **Provides transparency**

Reporting detailed methodological features improves transparency around how models were constructed.

- **Offers a stronger foundation for informed decisions**

By analyzing multiple dimensions (assumptions, parameters, methodological choices), the review provides a more solid basis for decision makers compared to simple outcome reporting.

DISCUSSION

- New diabetes medicines have changed treatment, especially for high-risk patients.
- Payers are cautious because these drugs are expensive and long-term benefits are still uncertain.
- Many GLP-1 and GIP/GLP-1 submissions were criticized for weak or indirect evidence.
- Real-world evidence strongly supports empagliflozin and gives it an advantage.
- HTA agencies in major countries are more **skeptical of GLP-1 and GIP/GLP-1 evidence.**
- **Empagliflozin** aligns best with what HTA bodies value: solid long-term outcomes and strong RWE.

CONCLUSION

- **Empagliflozin (SGLT2)** has the strongest and most reliable overall evidence.
- **GLP-1 RAs and tirzepatide** mainly improve HbA1c and weight, but these are only surrogate markers.
- HTA agencies frequently criticize GLP-1 and tirzepatide evidence.
- **Empagliflozin** has strong real-world validation (EMPRISE), proving real clinical impact.
- Cost-effectiveness evidence also favors empagliflozin.
- Overall, **empagliflozin** stands out as the most reliable and payer-aligned therapy.

FDA-Approved Empagliflozin Formulations

Brand Name	Brand Name	Formulation / Components	Dosage Form	Initial FDA Approval (US)	Primary Therapeutic Role
Jardiance®	Jardiance®	Empagliflozin (monotherapy)	Oral tablets (10 mg, 25 mg)	August 1, 2014	Glycemic control; Low CV death, HF and CKD
Glyxambi®	Glyxambi®	Empagliflozin + Linagliptin	Oral tablet	February 2, 2015	Dual glucose control (renal + incretin pathway)
Synjardy®	Synjardy®	Empagliflozin + Metformin (IR)	Oral tablet (immediate-release)	August 26, 2015	Improved insulin sensitivity + glucose excretion
Synjardy® XR	Synjardy® XR	Empagliflozin + Metformin (ER)	Oral tablet (extended-release)	December 12, 2016	Improved insulin sensitivity + glucose excretion
Trijardy® XR	Trijardy® XR	Empagliflozin + Linagliptin + Metformin (ER)	Oral tablet (extended-release)	January 27, 2020	Triple-mechanism control in advanced T2DM

THANK YOU