

RESEARCH MONOGRAPH . COMPOUND PROFILE

Empagliflozin

A highly selective SGLT2 inhibitor developed by Boehringer Ingelheim as an oral antihyperglycemic agent, distinguished from other gliflozins by the highest SGLT2-to-SGLT1 selectivity ratio in the class, landmark cardiovascular and renal outcome trial data, and regulatory approval across type 2 diabetes, heart failure with reduced and preserved ejection fraction, and chronic kidney disease.

DOCUMENT	KDC-MN-1560
ISSUED	2026-05-20
REVISION	1.0
AUTHOR	Kodiac bioLabs Research
COMPOUND CLASS	Selective sodium-glucose co-transporter 2 (SGLT2) inhibitor of the C-aryl glucoside structural class

ABSTRACT

Empagliflozin (BI 10773, marketed as Jardiance) is a potent, orally bioavailable, selective inhibitor of the sodium-glucose co-transporter 2 (SGLT2) protein expressed in the S1 and S2 segments of the renal proximal tubule, where it mediates approximately 90 percent of filtered glucose reabsorption. The compound is a C-aryl glucoside bearing a chlorophenyl core linked to a tetrahydrofuranyloxy-substituted benzyl moiety, and it exhibits the highest selectivity for SGLT2 over the intestinal isoform SGLT1 among the marketed gliflozins, with a selectivity ratio exceeding 2500-fold in heterologous expression systems. By inhibiting SGLT2, empagliflozin produces insulin-independent urinary glucose excretion of approximately 60 to 90 grams per day at therapeutic doses, resulting in reductions in fasting and postprandial plasma glucose, glycated hemoglobin (HbA1c), body weight, and systolic blood pressure without increasing hypoglycemia risk when used as monotherapy. Empagliflozin was developed by Boehringer Ingelheim in collaboration with Eli Lilly and Company, received initial regulatory approval in 2014 for the treatment of type 2 diabetes mellitus, and has since undergone one of the most consequential clinical development programs in modern cardiometabolic medicine. The EMPA-REG OUTCOME trial (2015), enrolling 7020 patients with type 2 diabetes and established cardiovascular disease, demonstrated a 38 percent relative risk reduction in cardiovascular death and a 35 percent reduction in hospitalization for heart failure, results that fundamentally altered the treatment paradigm for type 2 diabetes and prompted regulatory label expansions for cardiovascular risk reduction. The EMPEROR-Reduced trial (2020) demonstrated a

25 percent reduction in the composite of cardiovascular death or heart failure hospitalization in patients with heart failure and reduced ejection fraction regardless of diabetes status, while the EMPEROR-Preserved trial (2021) extended this benefit to patients with heart failure and preserved ejection fraction, a population for which few prior therapies had demonstrated efficacy. The EMPA-KIDNEY trial (2022) demonstrated a 28 percent reduction in the composite of kidney disease progression or cardiovascular death in 6609 patients with chronic kidney disease across a broad range of eGFR values. Pharmacokinetics are characterized by rapid oral absorption with peak plasma concentrations at approximately 1.5 hours, steady-state plasma protein binding of 80 to 86 percent, a terminal elimination half-life of approximately 12.4 hours supporting once-daily dosing, and metabolism predominantly through glucuronidation by UGT2B7, UGT1A3, UGT1A8, and UGT1A9 without clinically meaningful cytochrome P450 involvement. The compound has minimal drug-drug interaction potential and does not require dose adjustment for hepatic impairment or mild-to-moderate renal impairment, although efficacy on glycemic endpoints diminishes at lower eGFR values where the filtered glucose load is reduced. The principal adverse events are genital mycotic infections (occurring in approximately 5 to 10 percent of female patients and 1 to 5 percent of male patients), urinary tract infections, volume depletion (particularly in elderly patients and those on concomitant diuretics), and rare but serious events including euglycemic diabetic ketoacidosis and necrotizing fasciitis of the perineum (Fournier gangrene). This monograph reviews the chemistry, synthesis, and structural pharmacology of empagliflozin; the SGLT2 inhibitory mechanism in molecular and physiological detail; the comprehensive human pharmacokinetic record; the preclinical pharmacology across

metabolic, cardiovascular, and renal models; the landmark clinical evidence base spanning diabetes, heart failure, and chronic kidney disease; sourcing and quality verification; reconstitution and handling for research applications; stack-interaction considerations; adverse-event signal and safety profile; and a comparative assessment of five alternative SGLT2 inhibitors against empagliflozin on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Empagliflozin.

Marketed names: Jardiance (Boehringer Ingelheim/Eli Lilly; United States, European Union, Japan, Australia, and more than 100 additional jurisdictions). Combination products include Glyxambi (empagliflozin/linagliptin), Synjardy and Synjardy XR (empagliflozin/metformin), and Trijardy XR (empagliflozin/linagliptin/metformin).

Development codes: BI 10773 (Boehringer Ingelheim). The development code appears in the early pharmacology and Phase 1/2 clinical literature and on ClinicalTrials.gov registrations for the initial dose-finding studies [1].

Chemical Abstracts Service registry number: 864070-44-0.

International Union of Pure and Applied Chemistry name: (1S)-1,5-anhydro-1-C-[4-chloro-3-[[4-[[[(3S)-tetrahydro-3-furanyl]oxy]phenyl]methyl]phenyl]-D-glucitol. The compound is a C-aryl glucoside in which the glucose moiety is linked through a direct carbon-carbon bond to the aglycone aryl ring, conferring metabolic stability against hydrolysis by glucosidases that limited earlier O-glucoside SGLT2 inhibitors such as phlorizin.

1.2 Structural class and chemistry

Empagliflozin belongs to the C-aryl glucoside class of SGLT2 inhibitors, a structural series derived from the natural product phlorizin through sequential medicinal chemistry optimization to improve oral bioavailability, metabolic stability, and SGLT2 selectivity. The class includes dapagliflozin, canagliflozin, ertugliflozin, and sotagliflozin, all of which share the beta-D-glucopyranose pharmacophore linked through a carbon-carbon bond to a substituted aryl ring system [2].

Molecular formula: C₂₃H₂₇ClO₇.

Exact mass: 450.1446 g/mol (monoisotopic).

Molecular weight: 450.91 g/mol.

Physical properties: White to yellowish, non-hygroscopic crystalline powder. Freely soluble in dimethyl sulfoxide; soluble in methanol, ethanol, and acetonitrile; sparingly soluble in water at neutral pH. The compound is stable under standard storage conditions (room temperature, protected from moisture) for extended periods.

Stereochemistry: Empagliflozin contains multiple stereocenters: the glucitol moiety retains the D-glucose configuration with the (1S) absolute configuration at the anomeric carbon (the carbon-carbon bond to the aryl ring), and the tetrahydrofuranyl ether on the distal phenyl ring is the (3S) enantiomer. The compound is supplied as a single stereoisomer. Investigators acquiring research-grade empagliflozin should confirm stereochemical integrity by chiral high-performance liquid chromatography or optical rotation measurement.

1.3 Synthesis

The manufacturing synthesis of empagliflozin, as described by Wang et al. (2014) and implemented at metric-ton scale for commercial launch, proceeds through three principal stages [3]. First, a halogen-metal exchange reaction of an appropriately substituted aryl iodide (bearing the chloro and benzyloxy substituents) with isopropylmagnesium chloride generates the aryl Grignard reagent in tetrahydrofuran. Second, addition of this Grignard reagent to 2,3,4,6-tetra-O-pivaloyl-D-glucosyl lactone produces a lactol intermediate. Third, treatment of the lactol with hydrogen chloride in methanol generates the beta-anomeric methyl glycopyranoside, which is subsequently reduced with triethylsilane mediated by aluminum trichloride as a Lewis acid in dichloromethane/acetonitrile to afford the C-aryl glucoside with the required beta-configuration. The overall yield is approximately 50 percent across the three stages. Deprotection of the pivaloyl groups and installation of the (3S)-tetrahydrofuranyloxy ether (via nucleophilic aromatic substitution of a fluorophenyl intermediate with (S)-3-hydroxytetrahydrofuran) complete the synthesis. The final product is purified by recrystallization and characterized by nuclear magnetic resonance spectroscopy, mass spectrometry, and high-performance liquid chromatography to pharmaceutical-grade purity (greater than 99.5 percent). Radiolabeled ([¹⁴C] and [¹³C]) empagliflozin has been prepared in five steps from alpha-D-glucose in 34 percent overall yield for use in mass balance and metabolite identification studies [4].

2. Abstract

Empagliflozin (BI 10773) is a potent, selective, reversible inhibitor of the sodium-glucose co-transporter 2 (SGLT2) located in the brush border membrane of the S1 and S2 segments of the renal proximal tubule. The compound produces insulin-independent lowering of blood glucose by blocking the reabsorption of filtered glucose in the kidney, resulting in urinary glucose excretion (glucosuria) of approximately 60 to 90 grams per day at the 10 mg and 25 mg oral doses studied in clinical trials [5, 6]. The IC₅₀ for human SGLT2 inhibition is approximately 3.1 nanomolar, and selectivity over human SGLT1 exceeds 2500-fold, the highest among the marketed gliflozin class [7].

The principal registered indication is the treatment of type 2 diabetes mellitus, for which empagliflozin reduces HbA_{1c} by approximately 0.7 to 0.8 percentage points from baseline at the 10 mg and 25 mg doses, with concurrent reductions in body weight (approximately 2 to 3 kilograms) and systolic blood pressure (approximately 3 to 5 mmHg) [5, 6]. The glycemic, weight, and blood pressure effects are mechanistically linked: glucose excretion creates a caloric deficit (approximately 240 to 360 kcal per day), while the osmotic diuresis from glucosuria and natriuresis contributes to blood pressure reduction [8].

The clinical development of empagliflozin extended beyond glycemic control through a series of landmark cardiovascular and renal outcome trials. The EMPA-REG OUTCOME trial (Zinman et al. 2015) demonstrated a 14 percent reduction in major adverse cardiovascular events (MACE), a 38 percent reduction in cardiovascular death, a 35 percent reduction in hospitalization for heart failure, and a 32 percent reduction in all-cause mortality in patients with type 2 diabetes and established cardiovascular disease [9]. These results were the first demonstration that a glucose-lowering agent could reduce cardiovascular mortality in type 2 diabetes and catalyzed a paradigm shift in diabetes treatment guidelines worldwide.

The EMPEROR-Reduced trial (Packer et al. 2020) demonstrated a 25 percent reduction in the composite of cardiovascular death or hospitalization for worsening heart failure in 3730 patients with heart failure and reduced ejection fraction (left ventricular ejection fraction 40 percent or less), with benefit observed regardless of diabetes status [10]. The EMPEROR-Preserved trial (Anker et al. 2021) extended this

benefit to 5988 patients with heart failure and preserved ejection fraction (left ventricular ejection fraction greater than 40 percent), demonstrating a 21 percent reduction in the same composite endpoint [11]. The EMPA-KIDNEY trial (The EMPA-KIDNEY Collaborative Group, 2023) demonstrated a 28 percent reduction in the composite of kidney disease progression or cardiovascular death in 6609 patients with chronic kidney disease, with a 50 percent reduction in the rate of chronic eGFR decline [12].

These four landmark trials, together with the Phase 3 glycemetic efficacy program, have resulted in regulatory approvals for empagliflozin across type 2 diabetes, heart failure (both reduced and preserved ejection fraction), and chronic kidney disease in the United States, the European Union, Japan, and numerous additional jurisdictions. Empagliflozin is one of the most comprehensively studied cardiometabolic compounds of the past decade, with a clinical trial database encompassing more than 25,000 randomized patients.

3. Discovery and Development History

3.1 Origin

The SGLT2 inhibitor drug class traces its origin to phlorizin, a naturally occurring O-glucoside isolated from apple tree bark in 1835 and characterized as a competitive inhibitor of renal glucose reabsorption in the 1960s and 1970s [13]. Phlorizin produced glycosuria and normalized blood glucose in diabetic animal models but was limited by poor oral bioavailability, intestinal glucosidase-mediated hydrolysis of the O-glucoside bond, and non-selective inhibition of both SGLT1 and SGLT2 producing osmotic diarrhea. The medicinal chemistry strategy that produced the modern SGLT2 inhibitor class replaced the metabolically labile O-glucoside bond with a C-glucoside bond, conferring resistance to glucosidase hydrolysis and enabling oral administration [2].

Boehringer Ingelheim initiated a C-aryl glucoside medicinal chemistry program in the early 2000s targeting selective SGLT2 inhibition. Empagliflozin (BI 10773) emerged from this program as the clinical development candidate on the basis of its potency (IC₅₀ 3.1 nM at human SGLT2), exceptional selectivity over SGLT1 (IC₅₀ 8300 nM; selectivity ratio greater than 2500), favorable oral pharmacokinetic profile in preclinical species, and acceptable preclinical safety margins [1, 7]. The compound was patented in 2005 and advanced to preclinical development.

3.2 Clinical development

Phase 1 studies in healthy volunteers (2007 to 2008) characterized the dose-proportional pharmacokinetics, the dose-dependent urinary glucose excretion (up to approximately 90 grams per day at the highest doses), and the tolerability of single and multiple ascending doses [14]. Phase 2 studies (2009 to 2010) identified 10 mg and 25 mg as the optimal clinical doses on the basis of HbA_{1c} reduction, urinary glucose excretion, and tolerability [15]. An extensive Phase 3 program (2010 to 2013) evaluated empagliflozin as monotherapy and in combination with metformin, sulfonylureas, pioglitazone, and insulin across diverse patient populations, including those with renal impairment [5, 6, 16].

3.3 Regulatory approvals

Empagliflozin received its first regulatory approval in Australia in April 2014, followed by approval in the European Union in May 2014 and approval by the United States Food and Drug Administration in August 2014 for the treatment of type 2 diabetes mellitus at doses of 10 mg and 25 mg once daily [17]. The FDA required four postmarketing commitments, including a cardiovascular outcomes trial that became the EMPA-REG OUTCOME study.

3.4 Cardiovascular and renal indication expansions

The EMPA-REG OUTCOME results (published December 2015) led to FDA label expansion in December 2016 for the reduction of cardiovascular death in adults with type 2 diabetes and established cardiovascular disease, the first such indication for any glucose-lowering agent [9]. The EMPEROR-Reduced and EMPEROR-Preserved trial results led to FDA approval in August 2021 and February 2022, respectively, for the treatment of heart failure regardless of ejection fraction and regardless of diabetes status [10, 11]. The EMPA-KIDNEY trial results led to FDA approval in June 2023 for the treatment of chronic kidney disease at risk of progression [12]. In June 2023, the FDA also approved empagliflozin for type 2 diabetes in pediatric patients aged 10 years and older [18]. Empagliflozin is marketed globally as Jardiance by the Boehringer Ingelheim and Eli Lilly alliance.

The trajectory of empagliflozin from an antihyperglycemic agent to a cardiorenal medicine represents one of the most significant drug repositioning events in modern cardiovascular pharmacology. The EMPA-REG OUTCOME cardiovascular mortality signal, first reported at the European Association for the Study of Diabetes annual meeting in September 2015, was unexpected in magnitude and rapidity (separation of the Kaplan-Meier curves for cardiovascular death was visible within the first three months of treatment, suggesting a hemodynamic or metabolic mechanism rather than an anti-atherosclerotic effect) and catalyzed a reorientation of the entire SGLT2 inhibitor class toward heart failure and chronic kidney disease indications.

4. Mechanism of Action

Empagliflozin is a single-target pharmacological agent whose primary molecular activity is the selective, reversible inhibition of the sodium-glucose co-transporter 2 protein. The downstream metabolic, hemodynamic, and organ-protective consequences of SGLT2 inhibition are multiple and contribute differentially to the observed glycemic, cardiovascular, and renal effects.

4.1 SGLT2 physiology and inhibition

The sodium-glucose co-transporter 2 (SGLT2, encoded by the SLC5A2 gene) is a high-capacity, low-affinity transporter expressed almost exclusively in the apical membrane of the S1 and S2 segments of the renal proximal tubule [19]. Under normal physiological conditions, SGLT2 mediates the reabsorption of approximately 90 percent of the filtered glucose load (approximately 180 grams per day at normal plasma glucose and glomerular filtration rate), with the remaining 10 percent reabsorbed by the lower-capacity, higher-affinity SGLT1 transporter in the S3 segment. Under physiological conditions, essentially no glucose appears in the urine. In type 2 diabetes, SGLT2 expression and the renal glucose reabsorption capacity (the tubular maximum for glucose, TmG) are upregulated, contributing to the maintenance of hyperglycemia. This upregulation provides a direct therapeutic rationale for SGLT2 inhibition.

Empagliflozin binds reversibly to the glucose-binding site of SGLT2 with an IC₅₀ of approximately 3.1 nanomolar [7]. The binding competitively inhibits the co-transport of glucose and sodium across the apical membrane. At therapeutic plasma concentrations achieved by the 10 mg and 25 mg oral doses, empagliflozin inhibits approximately 30 to 50 percent of the filtered glucose reabsorption, resulting in urinary glucose excretion of 60 to 90 grams per day in patients with type 2 diabetes and normal renal function [5, 14]. The incomplete inhibition (relative to the theoretical maximum) reflects the compensatory upregulation of SGLT1 in the S3 segment and the pharmacokinetic profile of once-daily dosing.

4.2 Glycemic mechanism

The urinary glucose excretion produced by SGLT2 inhibition lowers both fasting and postprandial plasma glucose concentrations through a mechanism that is entirely independent of insulin secretion or insulin sensitivity [8]. This insulin independence distinguishes the gliflozin class from sulfonylureas, thiazolidinediones, GLP-1 receptor agonists, and DPP-4 inhibitors and accounts for the low intrinsic hypoglycemia risk when empagliflozin is used without concomitant insulin or insulin secretagogues. The glucosuric effect is self-limiting: as plasma glucose declines, the filtered glucose load decreases and glycosuria diminishes proportionally. The glycemic efficacy is dependent on glomerular filtration rate; as eGFR declines below 45 mL/min/1.73 m², the filtered glucose load diminishes and the glycosuric (and glycemic) efficacy of SGLT2 inhibition is attenuated. However, the cardiorenal benefits persist at eGFR values as low as 20 mL/min/1.73 m², indicating that the cardiovascular and renal protective effects are substantially independent of glycosuria [12].

4.3 Hemodynamic and cardiovascular mechanisms

The cardiovascular benefits of empagliflozin observed in EMPA-REG OUTCOME and the EMPEROR trials are not fully explained by glucose lowering alone and are the subject of active mechanistic investigation. Several proposed mechanisms, supported by varying degrees of preclinical and clinical evidence, include the following [20, 21]:

Osmotic diuresis and natriuresis. SGLT2 inhibition produces obligate sodium and water loss through the co-excretion of sodium with glucose. The resulting plasma volume contraction reduces cardiac preload and afterload and contributes to the blood pressure reduction of 3 to 5 mmHg observed in clinical trials. The preferential reduction of interstitial fluid volume relative to intravascular volume has been proposed as a mechanism for the early heart failure benefit.

Shift in myocardial substrate utilization. SGLT2 inhibition promotes a metabolic shift from glucose and fatty acid oxidation toward ketone body utilization (particularly beta-hydroxybutyrate) by the myocardium. Ketone bodies are a more oxygen-efficient fuel than fatty acids, and the shift may improve myocardial energetics in the failing heart [22].

Reduction in epicardial adipose tissue. Empagliflozin reduces epicardial and visceral adipose tissue volume, potentially reducing local paracrine inflammatory signaling to the myocardium [23].

Attenuation of cardiac fibrosis and remodeling. Preclinical studies in db/db mice and ZSF1 rats demonstrate that empagliflozin reduces cardiac interstitial fibrosis, pericoronary arterial fibrosis, and coronary arterial wall thickening [24, 25].

Inhibition of the sodium-hydrogen exchanger (NHE1). An off-target direct inhibitory effect on the cardiac sodium-hydrogen exchanger NHE1 has been proposed, which would reduce intracellular sodium and calcium overload in cardiomyocytes, although this mechanism remains debated [26].

4.4 Renal protective mechanisms

The renal benefits observed in EMPA-KIDNEY and in prespecified renal endpoints of EMPA-REG OUTCOME are attributed to the restoration of tubuloglomerular feedback [20]. SGLT2 inhibition increases sodium delivery to the macula densa in the distal tubule, activating tubuloglomerular feedback and producing afferent arteriolar vasoconstriction. This reduces intraglomerular pressure and glomerular hyperfiltration, a principal driver of progressive nephron loss in diabetic and non-diabetic chronic kidney disease. The initial hemodynamic effect manifests as a transient decline in eGFR of approximately 3 to 5 mL/min/1.73 m² in the first weeks of treatment, followed by stabilization and a slower rate of long-term eGFR decline compared to placebo. Additional renal mechanisms include reduction of proximal tubular workload (decreased sodium-glucose co-transport reduces oxygen consumption), attenuation of tubulointerstitial inflammation and fibrosis, and reduction of albuminuria [27].

4.5 Selectivity

Empagliflozin exhibits greater than 2500-fold selectivity for SGLT2 over SGLT1 and does not significantly inhibit other glucose transporters (GLUT1 through GLUT4) at therapeutic concentrations [7]. This high selectivity minimizes the risk of gastrointestinal adverse events associated with SGLT1 inhibition in the intestinal brush border (diarrhea, flatulence) and distinguishes empagliflozin from the less selective canagliflozin (approximately 250-fold) and the dual SGLT1/SGLT2 inhibitor sotagliflozin (approximately 20-fold).

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Empagliflozin is rapidly absorbed after oral administration, with peak plasma concentrations (C_{max}) reached at approximately 1.5 hours (t_{max}) post-dose [14, 28]. Plasma concentrations then decline in a biphasic manner, with a rapid distribution phase followed by a slower terminal elimination phase. Oral bioavailability is high; population pharmacokinetic analyses indicate near-complete absorption [28]. Administration with a high-fat, high-calorie meal decreases C_{max} by approximately 37 percent and AUC by approximately 16 percent, but this effect is not considered clinically meaningful and the drug may be administered without regard to food [17]. Pharmacokinetics are approximately dose-proportional over the 1 to 100 mg dose range studied in Phase 1 trials. Steady-state plasma concentrations are achieved within 5 to 6 days of once-daily dosing.

5.2 Distribution

The volume of distribution at steady state is approximately 73.8 liters, indicating moderate tissue distribution [28]. Plasma protein binding is 80.3 to 86.2 percent, predominantly to albumin. Red blood cell partitioning is moderate at 28.6 to 36.8 percent. The compound distributes to the kidney at concentrations sufficient to produce sustained SGLT2 inhibition throughout the dosing interval.

5.3 Metabolism

Empagliflozin is metabolized predominantly by glucuronidation catalyzed by uridine diphosphate-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9 [28, 29]. The three principal metabolites are the 2-O-glucuronide, 3-O-glucuronide, and 6-O-glucuronide conjugates, none of which has significant pharmacological activity at SGLT2 or other glucose transporters. Minor oxidative metabolic pathways are present but contribute minimally to overall clearance.

Critically, empagliflozin does not inhibit, inactivate, or induce cytochrome P450 (CYP) isoforms at clinically relevant concentrations [28]. This absence of CYP involvement is the molecular basis for the minimal drug-drug interaction potential observed in clinical pharmacokinetic studies and distinguishes the empagliflozin metabolic profile from compounds metabolized by polymorphic CYP enzymes. No dose adjustment is required based on UGT polymorphism status, although clinical investigations of UGT genetic variation effects on empagliflozin pharmacokinetics are ongoing [30].

5.4 Elimination

The terminal elimination half-life of empagliflozin is approximately 12.4 hours, supporting once-daily oral dosing [28]. Total clearance from plasma is approximately 10.6 liters per hour. Following administration of radiolabeled empagliflozin, 54.4 percent of radioactivity was recovered in urine and 41.1 percent in feces [29]. Unchanged empagliflozin accounted for approximately 43.5 percent of drug-related material in urine (23.7 percent of dose) and 82.9 percent of drug-related material in feces (34.1 percent of dose), indicating that both renal excretion of parent drug and biliary/fecal elimination contribute substantially to overall clearance.

Accumulation at steady state is minimal (accumulation ratio approximately 1.1 to 1.3), and clearance values at steady state are similar to those observed after single doses, confirming time-linear pharmacokinetics [28].

5.5 Routes of administration

Empagliflozin is administered exclusively by the oral route. The marketed formulation is a film-coated tablet containing 10 mg or 25 mg of empagliflozin. No parenteral, sublingual, or topical formulations have been developed for clinical use. For research applications, the compound may be dissolved in dimethyl sulfoxide (DMSO) for in vitro studies or suspended in vehicle (0.5 percent methylcellulose or similar) for oral gavage in animal studies.

5.6 Special populations

Renal impairment: Empagliflozin exposure (AUC) is modestly increased in patients with mild, moderate, and severe renal impairment (approximately 18 percent, 20 percent, and 66 percent increases, respectively), but no dose adjustment is recom-

mended [17]. Glycemic efficacy diminishes as eGFR declines below 45 mL/min/1.73 m² because the filtered glucose load is reduced; however, the cardiovascular and renal protective effects are maintained at lower eGFR values, as demonstrated in EMPA-KIDNEY [12].

Hepatic impairment: Empagliflozin exposure is modestly increased in patients with hepatic impairment (approximately 23 percent, 47 percent, and 75 percent increases in Child-Pugh A, B, and C, respectively), but these increases are not considered clinically meaningful and no dose adjustment is recommended [17].

Pediatric populations: Pharmacokinetic and pharmacodynamic studies have been conducted in pediatric patients aged 10 to 17 years with type 2 diabetes, with results supporting similar exposure-response relationships to those observed in adults [18].

Elderly populations: No clinically meaningful differences in pharmacokinetics have been observed in patients over 65 years of age; however, the risk of volume depletion-related adverse events is increased in the elderly and may warrant more careful monitoring when empagliflozin is co-administered with diuretics [17].

6. Preclinical Pharmacology

6.1 In vitro pharmacology

Empagliflozin inhibits human SGLT2 with an IC₅₀ of approximately 3.1 nanomolar and human SGLT1 with an IC₅₀ of approximately 8.3 micromolar, yielding a selectivity ratio of approximately 2680-fold [7]. In heterologous expression systems (HEK293 and CHO cells stably expressing human SGLT2), the compound produces concentration-dependent inhibition of alpha-methyl-D-glucopyranoside uptake with a steep Hill slope consistent with competitive inhibition at the glucose-binding site. Cross-species pharmacology demonstrates comparable potency against rat and mouse SGLT2, supporting the use of standard rodent models for preclinical evaluation [1].

6.2 Animal models of diabetes

In Zucker diabetic fatty (ZDF) rats, empagliflozin at oral doses of 1 to 10 mg/kg/day produced dose-dependent increases in urinary glucose excretion and reductions in fasting blood glucose, HbA_{1c}, and plasma triglycerides over 4 to 8 weeks of treatment [1]. In db/db mice (a model of type 2 diabetes with obesity), empagliflozin reduced blood glucose levels continuously throughout 7-day treatment periods, with significantly increased urinary glucose excretion, urine volume, and urinary sodium excretion observed from day 1 of dosing [24]. In diet-induced obesity mouse models, empagliflozin reduced body weight and fat mass associated with increased urinary glucose excretion, and lowered plasma cholesterol and liver triglyceride levels, demonstrating metabolic benefits beyond glucose lowering [31].

6.3 Cardiovascular preclinical pharmacology

In db/db mice, empagliflozin significantly ameliorated cardiac interstitial fibrosis, pericoronary arterial fibrosis, coronary arterial wall thickening, and cardiac macrophage infiltration [24]. The compound also improved vascular dilating function and increased the number and microvascular coverage of cardiac pericytes, suggesting direct protective effects on the coronary microvasculature independent of glucose lowering.

In ZSF1 rats (a model of metabolic syndrome with heart failure and preserved ejection fraction), empagliflozin improved systolic blood pressure, reduced left ventricular hypertrophy, ameliorated endothelial dysfunction, and attenuated cardiac remodeling [25]. In a non-diabetic porcine model of heart failure, empagliflozin improved left ventricular systolic function and reversed adverse remodeling, providing evidence for direct cardioprotective effects independent of glucose metabolism [32]. These preclinical findings preceded and are concordant with the cardiovascular benefits observed in the EMPEROR clinical trial program.

6.4 Renal preclinical pharmacology

In streptozotocin-induced diabetic rats and in diabetic Akita mice, empagliflozin reduced glomerular hyperfiltration, decreased albuminuria, and attenuated renal growth and glomerulosclerosis in proportion to the degree of hyperglycemia correction [33]. The renal protective mechanism in these models is consistent with the tubuloglomerular feedback hypothesis: increased sodium delivery to the macula densa reduces afferent arteriolar tone and intraglomerular pressure, limiting the hemodynamic stress on the glomerular filtration barrier. Additional preclinical work in non-diabetic 5/6 nephrectomy rat models of chronic kidney disease demonstrated that empagliflozin attenuated tubulointerstitial inflammation and fibrosis through mechanisms independent of glucose lowering, supporting the non-glycemic renal protective effects observed in EMPA-KIDNEY.

7. Clinical Evidence Base

7.1 Glycemic efficacy in type 2 diabetes

The Phase 3 clinical program for empagliflozin in type 2 diabetes comprised multiple randomized, double-blind, placebo-controlled trials evaluating the compound as monotherapy and in combination with other antidiabetic agents.

As monotherapy (24 weeks), empagliflozin 10 mg and 25 mg reduced HbA1c by 0.74 and 0.85 percentage points, respectively, from a baseline of approximately 7.9 percent, compared to a 0.08 percentage point increase with placebo [5]. Body weight decreased by 2.3 and 2.5 kilograms, and systolic blood pressure decreased by 2.9 and 3.7 mmHg.

As add-on to metformin (24 weeks), empagliflozin 10 mg and 25 mg reduced HbA1c by 0.70 and 0.77 percentage points versus placebo, with comparable weight and blood pressure effects [6]. As add-on to metformin plus sulfonylurea, add-on to pioglitazone, and add-on to basal insulin, the compound produced consistent HbA1c reductions of 0.5 to 0.8 percentage points across studies [16]. In an active-comparator trial versus the DPP-4 inhibitor sitagliptin, empagliflozin 25 mg was non-inferior at 24 weeks and statistically superior at 52 weeks on HbA1c reduction [5]. In a 104-week comparison with glimepiride as add-on to metformin, empagliflozin demonstrated comparable glycemic efficacy with significantly less weight gain and fewer hypoglycemic events [34].

7.2 EMPA-REG OUTCOME: cardiovascular outcomes in type 2 diabetes

The EMPA-REG OUTCOME trial (Zinman et al. 2015) was a randomized, double-blind, placebo-controlled trial that enrolled 7020 patients with type 2 diabetes and established cardiovascular disease (prior myocardial infarction, stroke, or peripheral arterial disease) across 590 sites in 42 countries [9]. Patients were randomized to empagliflozin 10 mg, empagliflozin 25 mg, or placebo, added to standard-of-care therapy. Median follow-up was 3.1 years.

The primary composite outcome (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke; 3-point MACE) occurred in 10.5 percent of patients in the pooled empagliflozin group versus 12.1 percent in the placebo group (hazard ratio 0.86; 95 percent confidence interval 0.74 to 0.99; $P = 0.04$). Cardiovascular death occurred in 3.7 percent versus 5.9 percent (hazard ratio 0.62; P less than 0.001). Hospitalization for heart failure occurred in 2.7 percent versus 4.1 percent (hazard ratio 0.65; $P = 0.002$). All-cause mortality occurred in 5.7 percent versus 8.3 percent (hazard ratio 0.68; P less than 0.001) [9].

The separation of Kaplan-Meier curves for cardiovascular death and heart failure hospitalization occurred within the first 3 months, substantially earlier than would be expected from glucose-lowering or atherosclerosis-modifying mechanisms, supporting hemodynamic and metabolic (rather than anti-atherosclerotic) mechanisms for the early benefit. Notably, nonfatal myocardial infarction and nonfatal stroke were not significantly reduced, consistent with this interpretation. Secondary renal endpoints showed a 39 percent reduction in incident or worsening nephropathy and a significantly slower rate of eGFR decline in the empagliflozin group [35].

7.3 EMPEROR-Reduced: heart failure with reduced ejection fraction

The EMPEROR-Reduced trial (Packer et al. 2020) enrolled 3730 patients with heart failure and left ventricular ejection fraction of 40 percent or less (New York Heart Association functional class II to IV) regardless of diabetes status, randomized to empagliflozin 10 mg or placebo [10]. Median follow-up was 16 months.

The primary composite outcome (cardiovascular death or hospitalization for worsening heart failure) occurred in 19.4 percent of the empagliflozin group versus 24.7 percent of the placebo group (hazard ratio 0.75; 95 percent confidence interval 0.65 to 0.86; P less than 0.001). The benefit was driven primarily by a reduction in heart failure hospitalization (30 percent reduction in total heart failure hospitalizations). The effect was consistent across subgroups defined by diabetes status, baseline ejection fraction, baseline eGFR, and concomitant therapy (including sacubitril/valsartan). The annual rate of decline in eGFR was slower in the empagliflozin group than in the placebo group (difference of 1.73 mL/min/1.73 m² per year) [10].

7.4 EMPEROR-Preserved: heart failure with preserved ejection fraction

The EMPEROR-Preserved trial (Anker et al. 2021) enrolled 5988 patients with heart failure and left ventricular ejection fraction greater than 40 percent (predominantly greater than 50 percent), randomized to empagliflozin 10 mg or placebo [11]. Median follow-up was 26.2 months.

The primary composite outcome occurred in 13.8 percent of the empagliflozin group versus 17.1 percent of the placebo group (hazard ratio 0.79; 95 percent confidence interval 0.69 to 0.90; P less than 0.001). As in EMPEROR-Reduced, the benefit was driven by a reduction in heart failure hospitalization. This trial was among the first to demonstrate a positive outcome for any pharmacological therapy in heart failure with preserved ejection fraction, a condition historically resistant to treatment [11]. Pre-specified pooled analyses across EMPEROR-Reduced and EMPEROR-Preserved confirmed consistent benefits across the full spectrum of left ventricular ejection fraction.

7.5 EMPA-KIDNEY: chronic kidney disease

The EMPA-KIDNEY trial (The EMPA-KIDNEY Collaborative Group, 2023) enrolled 6609 patients with chronic kidney disease (eGFR 20 to less than 45 mL/min/1.73 m², or eGFR 45 to less than 90 mL/min/1.73 m² with urine albumin-to-creatinine ratio 200 mg/g or greater), randomized to empagliflozin 10 mg or placebo [12]. The trial was stopped early for efficacy after a median follow-up of 2.0 years.

The primary composite outcome (kidney disease progression or cardiovascular death) occurred in 13.1 percent of the empagliflozin group versus 16.9 percent of the placebo group (hazard ratio 0.72; 95 percent confidence interval 0.64 to 0.82; P less than 0.001). The between-group difference in chronic eGFR slope (from 2 months to final follow-up) was 1.37 mL/min/1.73 m² per year, representing a 50 percent reduction in the rate of chronic eGFR decline. The benefit was consistent across subgroups defined by diabetes status, primary kidney disease etiology (diabetic kidney disease, glomerular disease, other causes), and baseline eGFR. Among participants without diabetes (54 percent of the cohort), the primary outcome was reduced by a comparable magnitude [12].

7.6 Additional clinical studies

Empagliflozin has been studied in additional clinical contexts including: the EMPULSE trial, demonstrating benefit when initiated in patients hospitalized for acute heart failure; the EMPA-TROPISM trial (Santos-Gallego et al. 2021), demonstrating cardiac reverse remodeling with improvement in left ventricular volumes and ejection fraction in non-diabetic patients with heart failure and reduced ejection fraction [32]; and ongoing studies in acute myocardial infarction, atrial fibrillation, and additional cardiorenal conditions. The breadth of ongoing clinical investigation reflects the pleiotropic organ-protective effects observed with SGLT2 inhibition.

8. Sourcing and Quality Verification

Pharmaceutical-grade empagliflozin is available as the marketed product Jardiance in film-coated tablets containing 10 mg or 25 mg. The pharmaceutical-grade material is manufactured by Boehringer Ingelheim under Good Manufacturing Practice conditions and is available by prescription in more than 100 jurisdictions worldwide.

Research-grade empagliflozin is supplied by multiple chemical and pharmaceutical research suppliers (Selleckchem, MedChemExpress, Cayman Chemical, Sigma-Aldrich/Merck, Toronto Research Chemicals, BocSciences, others) at greater than 98 percent purity by HPLC. Supply is in milligram to gram quantities as the anhydrous free form. Pricing is moderate, in the range of \$30 to \$150 per 100 milligrams of research-grade material at the time of monograph preparation, depending on supplier and quantity.

Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography area-percent purity, targeting greater than 98 percent
- Mass spectrometry confirmation of molecular weight (451.15 plus or minus 0.01 for the protonated molecule $[M+H]^+$)
- Nuclear magnetic resonance spectroscopy (1H and ^{13}C) confirmation of structural identity
- Chiral HPLC or optical rotation confirmation of stereochemical integrity at the glucitol anomeric center and the tetrahydrofuranyl ether stereocenter
- Karl Fischer titration for residual water content
- Residual solvent analysis by gas chromatography for common synthesis solvents

Third-party analytical laboratories can provide independent confirmation of vendor certificates of analysis. The research-grade empagliflozin market is well established owing to the compound's importance as a pharmacological tool and clinical reference standard.

9. Reconstitution and Handling

Empagliflozin is supplied as a white to yellowish crystalline powder for research applications. The compound is stable at room temperature under dry conditions and should be stored at 2 to 8 degrees Celsius for long-term storage with protection from moisture. The compound is non-hygroscopic and does not require desiccant protection under normal laboratory conditions.

For in vitro studies, stock solutions are typically prepared at 10 to 100 millimolar in dimethyl sulfoxide (DMSO). The compound is freely soluble in DMSO. Stock solutions in DMSO are stable for at least 6 months at minus 20 degrees Celsius and should be aliquoted for single-use to minimize freeze-thaw cycles. Working dilutions into aqueous cell culture media should maintain the final DMSO concentration below 0.1 percent (volume/volume) to avoid solvent toxicity. Aqueous solubility of the free form is limited (approximately 0.2 mg/mL at neutral pH); for aqueous stock solutions, the use of cyclodextrin-based solubilizers or co-solvent systems (polyethylene glycol 400, polysorbate 80) may improve dissolution.

For in vivo animal studies, empagliflozin is typically prepared as a suspension in 0.5 percent methylcellulose or hydroxypropyl methylcellulose for oral gavage administration. The standard preclinical oral dose range in rodent studies is 1 to 30 mg/kg/day. Suspensions should be freshly prepared or stored at 2 to 8 degrees Celsius and used within 7 days.

The pharmaceutical tablet formulation (Jardiance) is stable at room temperature (up to 25 degrees Celsius) with excursions permitted to 30 degrees Celsius, in the original blister packaging with protection from moisture [17]. Aliquoting of DMSO stock solutions for single-use is recommended; the compound is stable to at least 3 freeze-thaw cycles without measurable potency loss.

10. Stack Interactions and Combinations

Empagliflozin has minimal pharmacokinetic drug-drug interaction potential owing to its metabolism by glucuronidation (rather than CYP450 enzymes) and its absence of CYP inhibition or induction [28]. Formal pharmacokinetic interaction studies have demonstrated no clinically relevant interactions with metformin, linagliptin, sitagliptin, pioglitazone, glimepiride, warfarin, digoxin, ramipril, simvastatin, hydrochlorothiazide, torasemide, or oral contraceptives [17, 29]. Investigators conducting research with empagliflozin in combination with other compounds should nonetheless consider the following pharmacodynamic interactions:

Insulin and insulin secretagogues. Concurrent use with insulin, sulfonylureas, or meglitinides increases the risk of hypoglycemia. Dose reduction of the insulin or insulin secretagogue should be considered when initiating empagliflozin. In clinical trials, the incidence of hypoglycemia was approximately 2-fold higher in empagliflozin-treated patients on background insulin therapy compared to those on metformin alone [16].

Diuretics. Empagliflozin produces osmotic diuresis and natriuresis. Concurrent use with loop diuretics (furosemide, bumetanide, torsemide), thiazide diuretics (hydrochlorothiazide, chlorthalidone), or mineralocorticoid receptor antagonists (spironolactone, eplerenone, finerenone) may produce additive volume depletion, hypotension, and electrolyte disturbances. Clinical trials (EMPEROR-Reduced, EMPEROR-Preserved) enrolled patients on background diuretic therapy and demonstrated benefit with appropriate volume monitoring, but investigators should be aware of the additive diuretic effect [10, 11].

Renin-angiotensin-aldosterone system inhibitors. Concurrent use with ACE inhibitors or angiotensin receptor blockers is common in clinical practice and was the predominant background therapy in all pivotal empagliflozin trials. The combination is generally well tolerated but may produce additive effects on blood pressure and renal hemodynamics, particularly in volume-depleted patients.

UGT inducers. Rifampin, a strong UGT and CYP inducer, reduces empagliflozin AUC by approximately 35 percent through induction of UGT-mediated glucuronidation [29]. While no dose adjustment is formally recommended, the reduction in exposure may attenuate efficacy in patients on chronic rifampin therapy.

Other SGLT2 inhibitors. Concurrent use with another gliflozin is pharmacologically redundant and is not recommended. No clinical rationale for combination exists, and additive glucosuria would increase the risk of genital infections, volume depletion, and euglycemic ketoacidosis.

Lithium. Empagliflozin-induced natriuresis may theoretically affect lithium reabsorption in the proximal tubule. While no formal interaction study has been published, patients on lithium therapy should be monitored for changes in lithium levels when empagliflozin is initiated or discontinued.

GLP-1 receptor agonists. The combination of empagliflozin with GLP-1 receptor agonists (liraglutide, semaglutide, dulaglutide, tirzepatide) is increasingly used in clinical practice. The two classes act through complementary, non-overlapping mechanisms. No pharmacokinetic interaction has been identified, and the combination produces additive glycemic, weight, and cardiovascular benefits [36].

Digoxin. Empagliflozin produces a modest increase in digoxin exposure (AUC increase of approximately 6 percent) that is not clinically significant at standard doses [29].

11. Adverse Events and Safety

11.1 Common adverse events

The principal adverse events at registered doses (10 mg and 25 mg once daily), derived from pooled Phase 3 clinical trial data, are [5, 6, 17]:

- Genital mycotic infections (vulvovaginal candidiasis in women, balanitis and balanoposthitis in men): 5 to 10 percent in women, 1 to 5 percent in men, versus 1 to 2 percent on placebo. This is the most characteristic class effect of SGLT2 inhibitors and reflects glucosuria-promoted candidal overgrowth in the perineal environment. Most infections are mild to moderate, responsive to standard topical antifungal therapy, and rarely lead to drug discontinuation [17].
- Urinary tract infections: 7 to 9 percent, modestly higher than the 7 to 8 percent rate observed with placebo in clinical trials. Complicated urinary tract infections (pyelonephritis, urosepsis) are rare.
- Increased urination (pollakiuria, polyuria): 3 to 5 percent versus 1 percent on placebo. This is a pharmacological consequence of the osmotic diuresis and is generally self-limited.
- Volume depletion-related events (hypotension, dehydration, syncope): 0.5 to 1.0 percent overall, with higher rates in patients over 75 years of age and in those on concurrent diuretic therapy [17].
- Dyslipidemia: modest increases in LDL cholesterol of approximately 4 to 8 percent, attributed to hemoconcentration and metabolic substrate shifting.

11.2 Rare and serious adverse events

Euglycemic diabetic ketoacidosis. SGLT2 inhibitors, including empagliflozin, have been associated with diabetic ketoacidosis occurring at atypically low blood glucose concentrations (often less than 250 mg/dL) [37]. The mechanism involves SGLT2 inhibition-mediated reduction in insulin secretion and increase in glucagon secretion, promoting lipolysis and hepatic ketogenesis in the setting of absolute or relative insulin deficiency. The incidence is rare (approximately 0.5 to 1.0 per 1000 patient-years in clinical trials). Risk factors include low carbohydrate intake, dehy-

dration, acute illness, surgery, excessive alcohol intake, reduced insulin dose, and latent autoimmune diabetes of adulthood. Empagliflozin is not approved for type 1 diabetes, where the ketoacidosis risk is substantially higher. Current guidelines recommend temporary discontinuation of SGLT2 inhibitors at least 3 days before elective surgery.

Fournier gangrene (necrotizing fasciitis of the perineum). An FDA safety communication in August 2018 identified cases of Fournier gangrene associated with SGLT2 inhibitor use, including empagliflozin [38]. The condition is exceedingly rare but is life-threatening, requiring emergency surgical debridement and systemic antibiotics. The proposed mechanism involves the sustained perineal glucosuria creating a favorable environment for polymicrobial soft-tissue infection. The average time to onset was approximately 9 months after initiation of SGLT2 inhibitor therapy.

Acute kidney injury. Rare cases of acute kidney injury have been reported, particularly in the setting of volume depletion from concurrent diuretics, fever, or reduced oral intake. The mechanism is prerenal azotemia secondary to the osmotic diuresis. Empagliflozin should be withheld during periods of reduced oral intake or acute illness. Notably, the long-term renal effects of empagliflozin are protective, as demonstrated in EMPA-KIDNEY.

Lower extremity amputation. An increased risk of lower extremity amputation (primarily toe and forefoot) was observed with canagliflozin in the CANVAS program but has not been observed with empagliflozin in EMPA-REG OUTCOME or the EMPEROR trials [9, 10]. This is not a confirmed empagliflozin-specific risk.

11.3 Long-term safety

The combined clinical trial database of more than 25,000 randomized patients, with follow-up extending to 4 years in some trials, has not identified signals for malignancy (including bladder cancer), bone fracture, or hepatotoxicity [9, 10, 11, 12]. The overall discontinuation rate due to adverse events in the EMPEROR and EMPA-KIDNEY trials was similar between empagliflozin and placebo groups, supporting a favorable long-term tolerability profile.

11.4 Pregnancy and lactation

Empagliflozin is not recommended during pregnancy. Animal reproductive toxicity studies demonstrated adverse renal developmental effects (renal pelvic and tubule dilatation) in rats at exposures exceeding the maximum recommended human dose, consistent with the pharmacological mechanism of SGLT2 inhibition during the period of renal development [17]. No adequate human pregnancy data exist. The compound is present in the milk of lactating rats; human lactation data are not available, and the drug is not recommended during breastfeeding.

12. Comparative Assessment

This section presents a structured comparative assessment of five SGLT2 inhibitors against empagliflozin, evaluated against five competency standards: novelty, effect size, clinical trajectory (current regulatory state and evidence base), side-effect profile, and overall validation. The five comparators were selected as the principal SGLT2 inhibitors with substantive clinical evidence programs.

12.1 Dapagliflozin (Farxiga/Forxiga)

Mechanism: Selective SGLT2 inhibitor with approximately 1200-fold selectivity over SGLT1 [39]. The IC₅₀ for human SGLT2 is approximately 1.2 nanomolar.

Development trajectory: Developed by Bristol-Myers Squibb and AstraZeneca. The DECLARE-TIMI 58 cardiovascular outcomes trial (17,160 patients) demonstrated reduction in heart failure hospitalization but not MACE or cardiovascular death [40]. The DAPA-HF trial demonstrated benefit in heart failure with reduced ejection fraction [41]. The DELIVER trial demonstrated benefit in heart failure with preserved ejection fraction [42]. DAPA-CKD demonstrated benefit in chronic kidney disease [43].

Novelty: Low. The mechanism is identical to empagliflozin; dapagliflozin preceded empagliflozin to market.

Effect size: Glycemic efficacy is comparable to empagliflozin (HbA1c reduction approximately 0.7 to 0.8 percentage points). Cardiovascular death reduction was not demonstrated in DECLARE-TIMI 58 (in contrast to EMPA-REG OUTCOME), though heart failure hospitalization and renal endpoints showed benefit. DAPA-HF and DAPA-CKD effect sizes are comparable to those in the corresponding EMPEROR and EMPA-KIDNEY trials.

Side-effect profile: Similar to empagliflozin. No increased amputation or fracture risk.

Overall validation: High. Dapagliflozin has the broadest approved indication set alongside empagliflozin.

Comparison to empagliflozin: Dapagliflozin and empagliflozin are the two most comprehensively validated SGLT2 inhibitors. The principal differentiator is the EMPA-REG OUTCOME demonstration of cardiovascular mortality reduction, which was not replicated in DECLARE-TIMI 58 (though population differences may account for this). Empagliflozin has modestly higher SGLT2 selectivity. The two compounds are broadly interchangeable in clinical and research contexts.

12.2 Canagliflozin (Invokana)

Mechanism: SGLT2 inhibitor with the lowest selectivity among marketed selective gliflozins, approximately 250-fold over SGLT1 [39]. The partial SGLT1 inhibition at the 300 mg dose produces additional post-meal glucose lowering through delayed intestinal glucose absorption.

Development trajectory: Developed by Mitsubishi Tanabe and Janssen. First SGLT2 inhibitor approved by the FDA (2013). The CANVAS program (10,142 patients) demonstrated reduction in MACE but showed an unexpected doubling of lower extremity amputation risk [44]. The CREDENCE trial (4401 patients with diabetic kidney disease) demonstrated a 30 percent reduction in the composite renal endpoint [45].

Novelty: Low to moderate. The lower SGLT2 selectivity and partial SGLT1 activity distinguish canagliflozin pharmacologically.

Effect size: Glycemic efficacy at the 300 mg dose is modestly greater than empagliflozin 25 mg (HbA1c reduction approximately 0.9 to 1.0 percentage points), likely attributable to the additive intestinal SGLT1 inhibition. Cardiovascular and renal effect sizes are broadly comparable.

Side-effect profile: The principal distinguishing safety signal is the increased risk of lower extremity amputation (hazard ratio 1.97 in the CANVAS program), which has not been observed with empagliflozin [44]. An increased fracture risk was also observed.

Overall validation: Moderate to high. The CREDENCE trial provided strong renal evidence, but the amputation and fracture signals have reduced clinical uptake.

Comparison to empagliflozin: Empagliflozin has a substantially more favorable safety profile, with no amputation or fracture signals. Canagliflozin may offer modestly greater glycemic efficacy through SGLT1 inhibition but at the cost of a less fa-

vorable risk profile.

12.3 Ertugliflozin (Steglatro)

Mechanism: Highly selective SGLT2 inhibitor with approximately 2000-fold selectivity over SGLT1 [39]. Developed by Pfizer and Merck.

Development trajectory: Approved by the FDA in 2017 for type 2 diabetes. The VERTIS-CV cardiovascular outcomes trial (8246 patients) demonstrated non-inferiority to placebo on MACE but did not achieve superiority on any cardiovascular endpoint, including heart failure hospitalization [46].

Novelty: Low. The mechanism is identical to empagliflozin with comparable selectivity.

Effect size: The VERTIS-CV results were neutral for the primary MACE endpoint and for cardiovascular death. Heart failure hospitalization was reduced numerically but was not statistically confirmed. This neutral cardiovascular outcome profile distinguishes ertugliflozin unfavorably from empagliflozin and dapagliflozin.

Side-effect profile: Comparable to empagliflozin. No specific unique safety signal.

Overall validation: Low to moderate. The neutral cardiovascular outcome profile has limited clinical adoption. Merck announced market withdrawal of ertugliflozin.

Comparison to empagliflozin: Empagliflozin is strongly preferred over ertugliflozin on the basis of the demonstrated cardiovascular, heart failure, and renal outcome benefits.

12.4 Sotagliflozin (Inpefa)

Mechanism: Dual SGLT1/SGLT2 inhibitor with the lowest SGLT2-to-SGLT1 selectivity ratio in the class (approximately 20-fold) [47]. The substantial SGLT1 inhibition delays intestinal glucose absorption and produces additional postprandial glucose lowering, as well as incretin effects through increased distal intestinal glucose delivery.

Development trajectory: Developed by Lexicon Pharmaceuticals. The SOLOIST-WHF trial (1222 patients with diabetes and recent worsening heart failure) and the SCORED trial (10,584 patients with diabetes and chronic kidney disease) demonstrated reductions in cardiovascular death, heart failure hospitalization, and urgent heart failure visits [48, 49]. Approved by the FDA in 2023 for heart failure.

Novelty: High. The dual SGLT1/SGLT2 mechanism is pharmacologically distinct from the highly selective gliflozins and may confer additional gastrointestinal and incretin-mediated benefits.

Effect size: In SOLOIST-WHF, the primary composite endpoint was reduced by 33 percent (HR 0.67; P less than 0.001) [48]. Meta-regression analyses suggest that lower SGLT2 selectivity may be associated with superior heart failure outcomes relative to highly selective SGLT2 inhibitors, though head-to-head trials are lacking [50].

Side-effect profile: Higher rates of diarrhea and gastrointestinal adverse events compared to empagliflozin, attributable to intestinal SGLT1 inhibition. Genital infection rates are comparable.

Overall validation: Moderate. The evidence base is substantial for heart failure but smaller and less mature than the empagliflozin evidence base.

Comparison to empagliflozin: Sotagliflozin offers a pharmacologically distinct dual mechanism that may confer additional heart failure benefits. Empagliflozin has the substantially larger evidence base, the broader regulatory approval set, and the more favorable gastrointestinal tolerability profile.

12.5 Bexagliflozin (Brenzavvy)

Mechanism: Selective SGLT2 inhibitor with selectivity and potency comparable to empagliflozin [51].

Development trajectory: Developed by Theracos. Approved by the FDA in January 2023 for type 2 diabetes. No cardiovascular or renal outcome trial has been completed.

Novelty: Low. The mechanism is identical to the established SGLT2 inhibitor class.

Effect size: Glycemic efficacy is comparable to other SGLT2 inhibitors (HbA1c reduction approximately 0.6 to 0.8 percentage points). No cardiovascular or renal outcome data are available.

Side-effect profile: Comparable to other selective SGLT2 inhibitors in Phase 3 trials. Limited long-term safety data.

Overall validation: Low. The absence of cardiovascular and renal outcome data places bexagliflozin at a substantial evidence disadvantage.

Comparison to empagliflozin: Empagliflozin is strongly preferred on the basis of its landmark cardiovascular and renal outcome trial evidence. Bexagliflozin may serve as a lower-cost alternative for glycemic control but lacks the outcome evidence that drives contemporary SGLT2 inhibitor prescribing.

12.6 Comparator summary

The five comparator compounds occupy distinct positions in the SGLT2 inhibitor landscape. **Dapagliflozin** is the closest peer to empagliflozin, with comparable evidence across diabetes, heart failure, and chronic kidney disease, though lacking the cardiovascular mortality reduction demonstrated in EMPA-REG OUTCOME. **Canagliflozin** provides strong renal evidence (CREDENCE) but carries the amputation and fracture safety signals that limit its clinical position. **Ertugliflozin** has the weakest cardiovascular evidence (neutral VERTIS-CV) and has been withdrawn from some markets. **Sotagliflozin** offers a mechanistically distinct dual SGLT1/SGLT2 approach with promising heart failure data but a smaller evidence base and more gastrointestinal adverse events. **Bexagliflozin** is the newest entrant with no outcome data.

Empagliflozin occupies the strongest overall position in this comparator landscape by virtue of four large outcome trials (EMPA-REG OUTCOME, EMPEROR-Reduced, EMPEROR-Preserved, EMPA-KIDNEY) demonstrating benefit across the full spectrum of cardiometabolic and renal disease. It is the only SGLT2 inhibitor with demonstrated reduction in cardiovascular mortality in a dedicated outcomes trial, the only SGLT2 inhibitor with demonstrated benefit in both reduced and preserved ejection fraction heart failure in separate dedicated trials, and one of two (alongside dapagliflozin) with dedicated chronic kidney disease outcome trial evidence. The safety profile is among the most favorable in the class, without the amputation, fracture, or pronounced gastrointestinal signals observed with

canagliflozin and sotagliflozin. The high SGLT2 selectivity (greater than 2500-fold over SGLT1) minimizes off-target intestinal effects while maintaining the full renal and hemodynamic mechanism of SGLT2 inhibition.

13. References

1. Grempler R, Thomas L, Eckhardt M, et al. Empagliflozin, a novel selective sodium glucose cotransporter-2 (SGLT-2) inhibitor: characterisation and comparison with other SGLT-2 inhibitors. *Diabetes Obes Metab*. 2012;14(1):83-90.
2. Washburn WN. Development of the renal glucose reabsorption inhibitors: a new mechanism for the pharmacotherapy of diabetes mellitus type 2. *J Med Chem*. 2009;52(7):1785-1794.
3. Wang XJ, Zhang L, Byrne D, et al. Efficient synthesis of empagliflozin, an inhibitor of SGLT-2, utilizing an AlCl₃-promoted silane reduction of a beta-glycopyranoside. *Org Lett*. 2014;16(16):4090-4093.
4. Miao Z, Gao Y, Li X, et al. Synthesis of empagliflozin, a novel and selective sodium-glucose co-transporter-2 inhibitor, labeled with carbon-14 and carbon-13. *J Labelled Comp Radiopharm*. 2014;57(14):648-654.
5. Roden M, Weng J, Eilbracht J, et al. Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Diabetes Endocrinol*. 2013;1(3):208-219.
6. Haring HU, Merker L, Seewaldt-Becker E, et al. Empagliflozin as add-on to metformin in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. *Diabetes Care*. 2014;37(6):1650-1659.
7. Grempler R, Thomas L, Eckhardt M, et al. Empagliflozin, a novel selective sodium glucose cotransporter-2 (SGLT-2) inhibitor: characterisation and comparison with other SGLT-2 inhibitors. *Diabetes Obes Metab*. 2012;14(1):83-90.
8. Ferrannini E, Muscelli E, Frascerra S, et al. Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. *J Clin Invest*. 2014;124(2):499-508.
9. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117-2128.
10. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;383(15):1413-1424.

11. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*. 2021;385(16):1451-1461.
12. The EMPA-KIDNEY Collaborative Group. Empagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2023;388(2):117-127.
13. Ehrenkranz JR, Lewis NG, Kahn CR, Roth J. Phlorizin: a review. *Diabetes Metab Res Rev*. 2005;21(1):31-38.
14. Seman L, Macha S, Nehmiz G, et al. Empagliflozin (BI 10773), a potent and selective SGLT2 inhibitor, induces dose-dependent glucosuria in healthy subjects. *Clin Pharmacol Drug Dev*. 2013;2(2):152-161.
15. Heise T, Seewaldt-Becker E, Macha S, et al. Safety, tolerability, pharmacokinetics and pharmacodynamics following 4 weeks' treatment with empagliflozin once daily in patients with type 2 diabetes. *Diabetes Obes Metab*. 2013;15(7):613-621.
16. Haring HU, Merker L, Seewaldt-Becker E, et al. Empagliflozin as add-on to metformin plus sulfonylurea in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. *Diabetes Care*. 2013;36(11):3396-3404.
17. Jardiance (empagliflozin) tablets, for oral use. Prescribing Information. Boehringer Ingelheim Pharmaceuticals, Inc. Revised 2023.
18. Rascher W, Macha S, Engelen A, et al. Pharmacokinetics and pharmacodynamics of empagliflozin in paediatric patients aged 10-17 years with type 2 diabetes mellitus. *Br J Clin Pharmacol*. 2025;91(4):1178-1187.
19. Wright EM, Loo DD, Hirayama BA. Biology of human sodium glucose transporters. *Physiol Rev*. 2011;91(2):733-794.
20. Verma S, McMurray JJV. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. *Diabetologia*. 2018;61(10):2108-2117.
21. Lopaschuk GD, Verma S. Mechanisms of cardiovascular benefits of sodium glucose co-transporter 2 (SGLT2) inhibitors: a state-of-the-art review. *JACC Basic Transl Sci*. 2020;5(6):632-644.
22. Ferrannini E, Mark M, Mayoux E. CV protection in the EMPA-REG OUTCOME trial: a "thrifty substrate" hypothesis. *Diabetes Care*. 2016;39(7):1108-1114.

23. Sato T, Aizawa Y, Yuasa S, et al. The effect of dapagliflozin treatment on epicardial adipose tissue volume. *Cardiovasc Diabetol*. 2018;17(1):6.
24. Habibi J, Aroor AR, Sowers JR, et al. Sodium glucose transporter 2 (SGLT2) inhibition with empagliflozin improves cardiac diastolic function in a female rodent model of diabetes. *Cardiovasc Diabetol*. 2017;16(1):9.
25. Connelly KA, Zhang Y, Visber A, et al. Empagliflozin improves diastolic function in a nondiabetic rodent model of heart failure with preserved ejection fraction. *JACC Basic Transl Sci*. 2019;4(1):27-37.
26. Uthman L, Baartscheer A, Bleijlevens B, et al. Class effects of SGLT2 inhibitors in mouse cardiomyocytes and hearts: inhibition of Na⁺/H⁺ exchanger, lowering of cytosolic Na⁺ and vasodilation. *Diabetologia*. 2018;61(3):722-726.
27. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med*. 2016;375(4):323-334.
28. Scheen AJ. Pharmacokinetic and pharmacodynamic profile of empagliflozin, a sodium glucose co-transporter 2 inhibitor. *Clin Pharmacokinet*. 2014;53(3):213-225.
29. Macha S, Mattheus M, Halabi A, Pinnetti S, Woerle HJ, Broedl UC. Pharmacokinetics, pharmacodynamics and safety of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, in subjects with renal impairment. *Diabetes Obes Metab*. 2014;16(3):215-222.
30. ClinicalTrials.gov. Effect of glucuronosyltransferase (UGT) genetic variation on pharmacokinetics of empagliflozin. NCT05036421.
31. Steven S, Oelze M, Hanber A, et al. The SGLT2 inhibitor empagliflozin improves the primary diabetic complications in ZDF rats. *Redox Biol*. 2017;13:370-385.
32. Santos-Gallego CG, Requena-Ibanez JA, San Antonio R, et al. Empagliflozin ameliorates adverse left ventricular remodeling in nondiabetic heart failure by enhancing myocardial energetics. *J Am Coll Cardiol*. 2019;73(15):1931-1944.
33. Vallon V, Gerasimova M, Rose MA, et al. SGLT2 inhibitor empagliflozin reduces renal growth and albuminuria in proportion to hyperglycemia and prevents glomerular hyperfiltration in diabetic Akita mice. *Am J Physiol Renal Physiol*. 2014;306(2):F194-F204.

34. Ridderstrale M, Andersen KR, Zeller C, et al. Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: a 104-week randomised, active-controlled, double-blind, phase 3 trial. *Lancet Diabetes Endocrinol.* 2014;2(9):691-700.
35. Fitchett D, Zinman B, Wanner C, et al. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME trial. *Eur Heart J.* 2016;37(19):1526-1534.
36. Clegg LE, Penland RC, Engel SS, et al. Reduction in cardiovascular risk and improved estimated glomerular filtration rate with empagliflozin/linagliptin therapy. *Diabetes Obes Metab.* 2020;22(7):1094-1098.
37. Goldenberg RM, Berard LD, Cheng AYY, et al. SGLT2 inhibitor-associated diabetic ketoacidosis: clinical review and recommendations for prevention and diagnosis. *Clin Ther.* 2016;38(12):2654-2664.
38. U.S. Food and Drug Administration. FDA warns about rare occurrences of a serious infection of the genital area with SGLT2 inhibitors for diabetes. Drug Safety Communication. August 2018.
39. Abdul-Ghani MA, Norton L, DeFronzo RA. Renal sodium-glucose cotransporter inhibition in the management of type 2 diabetes mellitus. *Am J Physiol Renal Physiol.* 2015;309(11):F889-F900.
40. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2019;380(4):347-357.
41. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med.* 2019;381(21):1995-2008.
42. Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med.* 2022;387(12):1089-1098.
43. Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med.* 2020;383(15):1436-1446.
44. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med.* 2017;377(7):644-657.

45. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380(24):2295-2306.
46. Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. *N Engl J Med*. 2020;383(15):1425-1435.
47. Zambrowicz B, Freiman J, Brown PM, et al. LX4211, a dual SGLT1/SGLT2 inhibitor, improved glycemic control in patients with type 2 diabetes in a randomized, placebo-controlled trial. *Clin Pharmacol Ther*. 2012;92(2):158-169.
48. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med*. 2021;384(2):117-128.
49. Bhatt DL, Szarek M, Pitt B, et al. Sotagliflozin in patients with diabetes and chronic kidney disease. *N Engl J Med*. 2021;384(2):129-139.
50. Patoulias D, Papadopoulos C, Katsimardou A, et al. Influence of receptor selectivity on benefits from SGLT2 inhibitors in patients with heart failure: a systematic review and head-to-head comparative efficacy network meta-analysis. *Clin Res Cardiol*. 2022;111(4):428-440.
51. Halvorsen YD, Walford GA, Massaro J, et al. A 96-week, multinational, randomized, double-blind, parallel-group, clinical trial evaluating the safety and effectiveness of bexagliflozin in patients with type 2 diabetes. *BMJ Open Diabetes Res Care*. 2023;11(1):e003031.

This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly. Empagliflozin is approved by the United States Food and Drug Administration for the treatment of type 2 diabetes mellitus, heart failure, and chronic kidney disease at risk of progression. It is registered as a medicine in more than 100 jurisdictions worldwide. Investigators should consult their local regulatory authority before any research application.