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"Bexagliflozin: Clinical Efficacy, Safety, Pharmacology, and Medicinal Chemistry of a Novel SGLT2 Inhibitor for Type 2 Diabetes."

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Abstract: *Bexagliflozin is a highly potent and selective sodium–glucose co-transporter-2 (SGLT2) inhibitor approved for the treatment of type 2 diabetes mellitus. Structure–activity relationship (SAR) analysis indicates that the drug consists of a glycone moiety linked to a biaryl aglycone domain containing central and peripheral phenyl rings, in which the R_1 and R_2 substituents modulate binding affinity and metabolic stability. The parent compound demonstrates strong SGLT2 inhibition ($IC_{50} \approx 2.3$ nM), whereas systematic substitution on the aglycone rings alters potency. Metabolic profiling reveals two principal Phase I/Phase II pathways: renal UGT1A9-mediated glucuronidation and hepatic CYP3A4-mediated hydroxylation, producing glucuronide and hydroxy metabolites with substantially reduced SGLT2 inhibitory activity (IC_{50} values >10,000 nM and >18 nM, respectively). These findings support that metabolic inactivation is rapid and the formation of inactive metabolites contributes to the drug's favorable safety profile. The synthetic route to bexagliflozin, as described in U.S. Patent US7838499B2, comprises multi-step coupling, azide reduction, and Suzuki-type cross-coupling reactions affording final material in high overall yield. Together, the SAR, metabolism, and synthetic data highlight the structural determinants governing bexagliflozin potency, metabolic fate, and drug-like properties and provide a foundation for the further optimization of SGLT2 inhibitor scaffolds.*

Keywords: SGLT2 inhibitors; bexagliflozin; SAR; C-glycosides; medicinal chemistry; phenyl substitution; metabolic stability; synthetic route

I. INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a rapidly growing metabolic disease characterized by hyperglycemia resulting from a combination of insulin resistance and declining pancreatic insulin secretion, ultimately impairing glucose uptake and elevating blood glucose concentrations. [1] Poorly controlled T2DM contributes to substantial morbidity and mortality through complications such as coronary heart disease, chronic kidney disease, diabetic retinopathy, neuropathy and cardiovascular events, and currently affects over 10.5% of adults worldwide, with projections reaching 12.2% by 2045. [2] The global burden is reflected not only in premature mortality over 6.5 million deaths in 2021 but in the massive financial strain, given diabetes-related expenditures approaching 966 billion USD in 2021 and expected to exceed 1054 billion USD by 2045. Standard pharmacotherapeutic options include insulin, metformin, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, GLP-1 receptor agonists, and sodium-glucose cotransporter-2 (SGLT2) inhibitors, each with distinct benefits, risks, and rising costs; notably, national glucose-lowering medication expenditures increased 240% between 2005–2007 and 2015–2017, with dramatic cost surges for insulin and newer agents. SGLT2 inhibitors represent a mechanistically unique drug class that reduces plasma glucose by inhibiting renal glucose reabsorption in the proximal tubule, promoting glycosuria and natriuresis independently of insulin secretion, while providing additional benefits such as weight loss, blood pressure reduction, renoprotection, and reductions in heart failure hospitalizations and cardiovascular mortality. [3] In January 2023, the FDA approved bexagliflozin marketed as

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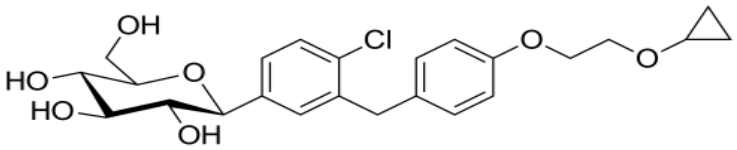
Brenzavvy by TheracosBio as the fifth orally administered SGLT2 inhibitor for T2DM adjunctive to diet and exercise, based on successful clinical evidence demonstrating glycemic efficacy, cardiovascular and renal advantages, and a favorable safety profile. Bexagliflozin is administered as a 20 mg once-daily tablet, offers significant cost advantages relative to other SGLT2 inhibitors, and, although not approved for chronic kidney disease or type 1 diabetes, has demonstrated usefulness in CKD populations while avoiding insulin-dependent mechanisms, making it a valuable therapeutic alternative for patients with longstanding T2DM and high metabolic and cardiovascular risk. [4]

Table 1: Drug Information Summary

Category	Details
Drug names	Brand: Brenzavvy™ • Generic: Bexagliflozin
Structure	
IUPAC Name	(2S,3R,4R,5S,6R)-2-[4-chloro-3-[[4-(2-cyclopropoxyethoxy) phenyl]methyl]phenyl]phenyl]-6-(hydroxymethyl)oxane-3,4,5-triol
Indications	Treatment of T2DM
Mechanism of Action	Highly selective SGLT2 inhibitor that inhibits renal reabsorption of glucose in the proximal tubule
Pharmacokinetics – Absorption	• Cmax: 134 ng/mL • Tmax: 2–4 h • AUC: 162 ng·h/mL
Distribution	• Vd: 262 L • Plasma Protein Binding: 93%
Metabolism	Major metabolism via UGT1A9 to pharmacologically inactive 3′-O-glucuronide; CYP3A4 oxidation to oxidized metabolites
Elimination	• Oral Bioavailability: ~78% • Half-Life: 12 h • Fecal: ~51% (parent 28.7%) • Renal: ~41% (1.5% parent; 30.1% metabolite EGT0002149) • Clearance: 19.1 L/h
Major Side Effects	Urinary tract infections, ketoacidosis, volume depletion, genital mycotic infections, necrotizing fasciitis
Regulatory Approval	FDA approval date: January 20, 2023

Bexagliflozin drug for treating type 2 diabetes mellitus: [62-68]

Bexagliflozin received FDA approval on the basis of several clinical trials in which the drug was examined as monotherapy, in combination with metformin, or as an add-on to standard oral and injectable antidiabetic treatments. These regimens included metformin, sulfonylureas, insulin, DPP-4 inhibitors, or multidrug combinations. Across multiple phase 3 studies, the drug consistently improved glycemic parameters, with significant reductions in HbA1c and fasting plasma glucose. Modest decreases in systolic blood pressure and body weight were also observed.

Some trials specifically enrolled individuals with type 2 diabetes accompanied by chronic kidney disease (CKD) or coronary heart disease (CHD). In patients with diabetes and CKD, renal function was largely preserved, with only mild changes in serum creatinine (an increase of ~0.08 mg/dL) and estimated GFR (a decrease of ~2.4 mL/min/1.73 m² at week 24). In the CHD cohort, bexagliflozin reduced the rate of hospitalization for heart failure among participants with a prior history of heart failure (5% vs. 9% with placebo) and lowered all-cause mortality (3.45% vs. 4.59% with placebo). Rates of major adverse cardiovascular events were also numerically lower compared with placebo. While these findings are encouraging, further studies are required to determine whether bexagliflozin can be firmly positioned as a therapeutic option for heart failure.

Comparative studies indicated statistically significant superiority ($P < 0.05$) over glimepiride, sitagliptin, and dapagliflozin with respect to improvements in HbA1c, fasting glucose, body weight, and systolic blood pressure.

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Beyond human medicine, bexagliflozin is also marketed as Bexacat, becoming the first SGLT2 inhibitor approved for veterinary use, specifically in diabetic cats. In a small study involving five poorly regulated diabetic cats, Bexacat use for four weeks led to significant reductions in insulin requirements; two cats discontinued insulin entirely. Fasting glucose levels improved, and adverse effects were mild without episodes of hypoglycemia.

Despite its therapeutic benefits, bexagliflozin is associated with adverse effects characteristic of the SGLT2 inhibitor class. Ketoacidosis represents a notable and potentially life-threatening complication that can occur even at relatively modest glucose levels (<250 mg/dL). Additional concerns include lower-limb complications such as infections, gangrene, osteomyelitis, ischemia, and a potential signal for increased amputation risk. Intravascular volume depletion may also lead to hypotension, transient renal function changes, or, in severe cases, acute kidney injury. The drug class has also been linked to serious urinary tract infections (including urosepsis and pyelonephritis), genital fungal infections, and rare necrotizing infections such as Fournier's gangrene, all of which require urgent medical intervention. Furthermore, when used with insulin or insulin secretagogues, hypoglycemia may occur; dose adjustments to concurrent antidiabetic agents are therefore recommended.

In summary, type 2 diabetes remains a major global health burden despite progress in pharmacologic treatment. SGLT2 inhibitors represent an important step forward, and bexagliflozin adds to this therapeutic class with demonstrated glycemic efficacy and additional metabolic and cardiovascular benefits. However, the current evidence base remains limited, and more comprehensive investigations—particularly head-to-head comparisons with other SGLT2 inhibitors and dedicated studies in individuals with CKD or CHD—are warranted to better define its safety profile, comparative effectiveness, and potential role in heart failure management.

Table No. 1: Major outcomes of clinical studies [62-68]

Study	Population / Comparator	Dose	HbA1c (%)	FPG (mmol/L)	Body Mass (kg)	SBP (mmHg)
Allegretti et al.	Placebo	–	–0.24	–0.76	–1.61	–3.8
	Bexagliflozin	20 mg	–0.61	+1.50	+0.45	–0.55
Halvorsen et al.	Placebo	–	–0.53	–1.58	–2.41	–4.90
	Bexagliflozin	20 mg	–0.55	–1.58	–0.14	–1.97
Halvorsen et al.	Placebo	–	+0.24	–0.11	–0.38	–4.15
	Bexagliflozin	5–20 mg	–0.31 to –0.56	–0.96 to –1.18	–1.58 to –1.89	–4.15 to –6.36
BEST trial	Placebo	–	–0.37	+0.06	–3.03	–6.87
	Bexagliflozin	20 mg	–0.85	–1.33	–0.81	–9.83
Halvorsen et al.	Sitagliptin	100 mg	–0.82	–1.45	–3.35	–1.90
	Bexagliflozin	20 mg	–0.74	–1.82	+0.60	–4.23
McMurray et al.	Glimepiride	2 mg	–0.66	–0.91	–3.75	–7.18
	Bexagliflozin	20 mg	–0.74	–1.30	–2.22	–13.43
Xie et al.	Dapagliflozin	10 mg	–1.08	–1.87	–2.52	–6.3
	Bexagliflozin	20 mg	–1.10	–1.95	–2.52	–6.4

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Table 2. Adverse Events of Bexagliflozin Clinical Studies [62-68]

Study	Population / Comparator	Dose	Total Patients Affected, n (%)	Serious Adverse Events, n (%)	Hypoglycemia, n (%)	Urinary Tract Infections, n (%)	Genital Mycotic Infections, n (%)	Other Notable Adverse Events
Allegretti et al.	Placebo	–	105 (67.7%)	9 (5.8%)	38 (24.5%)	5 (3.2%)	0 (0%)	Musculoskeletal: 6 (3.9%); Other: 7 (4.5%)
	Bexagliflozin	20 mg	109 (69.4%)	11 (7%)	39 (24.8%)	11 (7.0%)	5 (3.2%)	Musculoskeletal: 7 (4.5%); Other: 7 (4.5%)
Halvorsen et al.	Placebo	–	94 (66.7%)	12 (8.5%)	25 (17.7%)	21 (14.5%)	2 (1.4%)	Musculoskeletal: –; Other: –
	Bexagliflozin	20 mg	93 (64.1%)	4 (2.8%)	24 (16.6%)	21 (14.5%)	2 (1.4%)	Musculoskeletal: –; Other: –
Halvorsen et al.	Placebo	5–20 mg	29–36 (40–47%)	1–2 (1.4–2.8%)	1–4 (1.4–5.3%)	1–2 (1.4–2.8%)	1–2 (1.4–2.8%)	Musculoskeletal: 2–4 (2.8–5.6%); Other: 12–15 (16.7–20.8%)
BEST trial	Placebo	–	594 (104.8%)	26 (4.6%)	10 (5.2%)	4 (2.1%)	0 (0%)	Other disorders: 35 (18.1%)
	Bexagliflozin	20 mg	1112 (98.2%)	373 (33%)	6 (3.1%)	7 (3.7%)	5 (2.6%)	Other disorders: 18 (9.4%)
Halvorsen et al.	Sitagliptin	100 mg	197 (102.1%)	4 (2.1%)	10 (5.2%)	7 (3.7%)	5 (2.6%)	Other disorders: 18 (9.4%)
Halvorsen et al. [18]	Glimepiride	2 mg	173–213 (81.2–80.8%)	7 (3.7%)	71 (33.3%)	25 (11.7%)	20 (9.4%)	Other disorders: 44 (20.7%)
Xie et al.	Dapagliflozin	10 mg	132 (65.0%)	7 (3.5%)	8 (3.9%)	16 (7.9%)	11 (5.4%)	Other disorders: 35 (17.2%)
	Bexagliflozin	20 mg	127 (62.6%)	9 (4.4%)	19 (9.4%)	13 (6.4%)	12 (5.9%)	Other disorders: 27 (13.3%)

Clinical importance of bexagliflozin as a T2DM medication

SGLT2 inhibitors have become an important therapeutic option for patients with T2DM, particularly because most conventional glucose-lowering agents do not address the high risk of chronic kidney disease (CKD) that accompanies longstanding diabetes. Although the class is known to improve glycemic control and slow renal decline, their glucose-lowering efficacy typically decreases as kidney function progressively worsens. Notably, emerging evidence indicates that bexagliflozin may retain its therapeutic benefit in patients with moderate CKD, including those with CKD stages 3a and 3b, a finding not consistently observed with other SGLT2 inhibitors. To date, few studies have demonstrated significant reductions in HbA1c levels in patients with CKD stage 3b, highlighting a potential advantage for bexagliflozin in this subset of patients. [5,6] Mechanistically, bexagliflozin is characterized by high selectivity for the SGLT2 transporter relative to SGLT1, a distinction that may enhance glucose-lowering efficacy while minimizing off-target gastrointestinal effects associated with SGLT1 inhibition. Despite these benefits, the drug remains contraindicated in patients receiving dialysis, where renal impairment is too advanced for therapeutic benefit. [7,8]

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Renal effects further distinguish bexagliflozin from other agents in its class. A comparative meta-analysis suggested that bexagliflozin may lead to a more pronounced initial decline in estimated glomerular filtration rate (eGFR), thought to reflect its vasoconstrictive action on the afferent renal arteriole. This reduction in intraglomerular pressure mitigates hyperfiltration and is believed to confer long-term renal protection, similar to the mechanism proposed for other SGLT2 inhibitors. Among available therapies, only luseogliflozin approved in Japan but not in the United States demonstrates a comparable renal signature. [9, 10] Beyond renal outcomes, bexagliflozin also appears advantageous with respect to hypoglycemia risk. In a 96-week trial comparing bexagliflozin with the sulfonylurea glimepiride as add-on therapy to metformin, bexagliflozin was associated with 35% fewer hypoglycemic events and achieved sustained HbA1c reductions of approximately 0.8% early in treatment and 0.6% at study completion. Although head-to-head clinical comparisons with other SGLT2 inhibitors are lacking, available data indicate that bexagliflozin provides similar improvements in fasting plasma glucose, HbA1c, and body weight, with a safety profile consistent with the drug class. [11] Common adverse events include urinary tract infections, female genital fungal infections, volume depletion, and rare ketoacidosis, reflecting the known pharmacologic effects of SGLT2 inhibition. [12]

Cardio protective nature of SGLT2 inhibitors

Beyond their established role in lowering blood glucose, SGLT2 inhibitors have demonstrated significant cardioprotective effects that appear to be independent of glycemic control. Recent studies have reported reductions in heart failure events, with proposed mechanisms involving suppression of sympathetic nervous system activity and reductions in both cardiac preload and afterload. [13] These effects have been linked to modulation of the free fatty acid receptor 3 (FFAR3), a receptor expressed on sympathetic neurons that enhances myocardial stimulation via norepinephrine release when activated. [14] SGLT2 inhibition increases circulating β-hydroxybutyrate, a ketone body typically elevated during fasting, which in turn attenuates FFAR3-mediated sympathetic signaling, thereby mitigating cardiac stress. While dapagliflozin has been the most thoroughly investigated agent within the class for cardiovascular outcomes, accumulating evidence suggests that increases in ketone body production and associated cardioprotective effects represent a class-wide phenomenon. [15]

At present, bexagliflozin carries no formal indication for the treatment of cardiovascular disease or heart failure, distinguishing it from some other SGLT2 inhibitors currently used in these clinical settings. [16] Nevertheless, emerging clinical data indicate that bexagliflozin may exert favorable cardiovascular effects. Studies evaluating its use alongside metformin have shown statistically significant reductions in systolic blood pressure and improved glycemic control compared to metformin monotherapy. [17] Findings from the Bexagliflozin Efficacy and Safety Trial (BEST) further support the potential cardioprotective profile of the drug, noting reductions in systolic blood pressure among patients with elevated cardiovascular risk. Although these results are preliminary and ongoing trials are needed to clarify long-term outcomes, the evidence to date suggests that bexagliflozin may confer beneficial cardiovascular effects similar to other agents in the SGLT2 class. [18]

Structural modifications of SGLT2 inhibitors

All currently available SGLT2 inhibitors are structurally derived from phlorizin, a natural compound originally isolated from apple tree bark. Phlorizin was first used as an antipyretic treatment for fevers and malaria, [19] and in 1886 von Mering observed that its administration induced glycosuria. [20] Decades later, research into the molecular mechanism underlying phlorizin's effects helped establish the basis for the development of modern SGLT2 inhibitors.46,48 Early studies demonstrated that phlorizin improved insulin sensitivity and lowered blood glucose levels. [21] However, despite these promising metabolic effects, phlorizin was unsuitable as a therapeutic hypoglycemic agent due to several limitations. As a non-selective SGLT inhibitor capable of blocking both SGLT1 and SGLT2, its use was associated with significant gastrointestinal adverse effects, including diarrhea and dehydration. [22]

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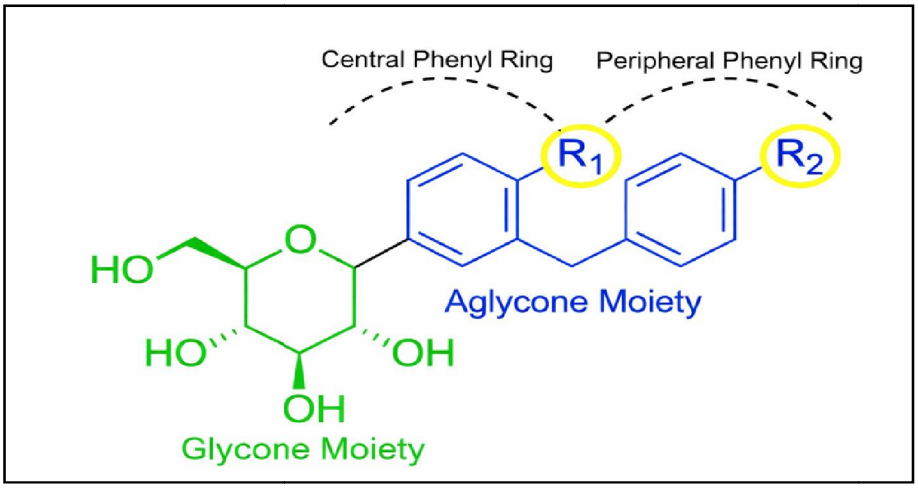

Fig. 1: Structural activity relationship of bexagliflozin

Phlorizin also exhibited poor metabolic stability after oral administration because its O-glucoside structure was rapidly degraded by β-glucosidase enzymes. [23] To overcome this barrier, medicinal chemistry efforts replaced the O-glucoside with N- or C-glucoside linkages, greatly improving metabolic stability. [24] This modification led to the development of the current family of SGLT2 inhibitors, all of which incorporate a C-glycosidic linkage connecting a central phenyl group to a glucose moiety.

The core structure of SGLT2 inhibitors consists of four components: a glycone moiety, an aglycone moiety, a central phenyl ring, and a peripheral phenyl ring. [25] Structural modifications to these regions influence drug potency, receptor affinity, and selectivity between SGLT2 and SGLT1. [26] The glycone moiety, which typically remains unmodified, participates in binding to the SGLT2 receptor's glucose pocket and effectively blocks glucose reabsorption. One notable exception is luseogliflozin, whose glycone contains a sulfur atom instead of oxygen, enhancing inhibitory activity. [27]

The C-glycosidic linkage connecting the glycone and aglycone confers substantially greater metabolic stability compared with an O-glycosidic linkage. Additional structure activity relationships are driven by substituents on the aglycone moiety. Small halogenated or alkyl groups at the R1 position increase potency and selectivity, whereas bulkier groups tend to reduce activity. [28] A chlorine substituent at R1 on the central phenyl ring has been identified as an optimal modification for enhancing potency. The distance between the central and peripheral phenyl rings also modulates activity; the preferred spacing appears to be a single-carbon linker, as both shortening and lengthening this linkage diminish inhibitory effects. [29]

Alterations to the peripheral phenyl ring influence both potency and selectivity. For example, replacing the phenyl ring with thiophene, as in canagliflozin, increases both SGLT2 affinity and inhibitory potency. Ipragliflozin utilizes a benzothiophene group instead, resulting in reduced potency but improved selectivity. Collectively, these observations suggest that sulfur-containing heterocycles may enhance overall inhibitory performance. [30]

The R2 substituent further differentiates SGLT2 inhibitors by affecting their potency and receptor selectivity. Lipophilic electron-withdrawing groups such as halogens or weak electron-donating groups, including the cyclopropyloxyethoxy moiety found in bexagliflozin, confer particularly strong activity. Increasing the length of the R2 group enhances potency, but often at the cost of reduced selectivity for SGLT2 over SGLT1. [31]

Variance in moieties of bexagliflozin

Bexagliflozin is structurally related to the previously approved SGLT2 inhibitor dapagliflozin, with the major difference residing at the R2 position on the peripheral phenyl ring. Whereas dapagliflozin incorporates an ethoxy group at this site, bexagliflozin contains a bulkier cyclopropyloxyethoxy substituent. Structure activity studies

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comparing a series of analogues with modifications at the R2 tail demonstrate how these variations influence both potency and selectivity. the cyclopropyloxyethoxy analogue exhibited excellent SGLT2 inhibitory potency with high selectivity relative to SGLT1. A similar profile was observed for the cyclobutyloxyethoxy analogue, which showed nearly identical IC50 values. However, increasing the size of the cycloalkyl ring beyond these substitutions led to a decrease in potency, indicating that the smaller cyclopropyl group may provide an optimal spatial configuration for balancing potency and selectivity. [32]

Bexagliflozin also features a lipophilic, electron-withdrawing R1 substituent, a modification previously shown to enhance SGLT2 inhibition. This functional group plays a key role in potency but does not substantially impact selectivity between SGLT2 and SGLT1. [33]

Synthesis of bexagliflozin

TheracosBio, LLC. filed a product patent in 2010 that dis- played information about the discovery and synthesis of bexagliflozin. The synthesis outlined in patent US7838499B2 includes 5 steps to achieving a yield of 10% (Fig. 3). The synthesis starts by creating 2-cyclo- propoxyethanol by reacting 2-(2-bromoethyl)-1,3- dioxolane with magnesium and dibromoethane in tetrahydrofuran (THF). The compound 2-cyclo propoxyethanol which results from the prior reaction, is then tosylated to form molecule. The aglycone moiety is then used in a Br/Li exchange reaction and added to the glycone moiety. Then, mesylation of the hydroxyl group of the intermediate from the reaction with the glycone moiety will form compound. The last step removes the methoxy group from by utilizing the reducing agent Et3SiH and BF3×Et2O which forms bexagliflozin after treatment with L-proline. High-performance liquid chro- matography (HPLC) results show an achieved purity of 99.2% of bexagliflozin [34]. A major disadvantage of using this route for synthesis is the requirement of the correct stereoisomer for molecule by using a preparative HPLC strategy which decreases the overall product yield [34].

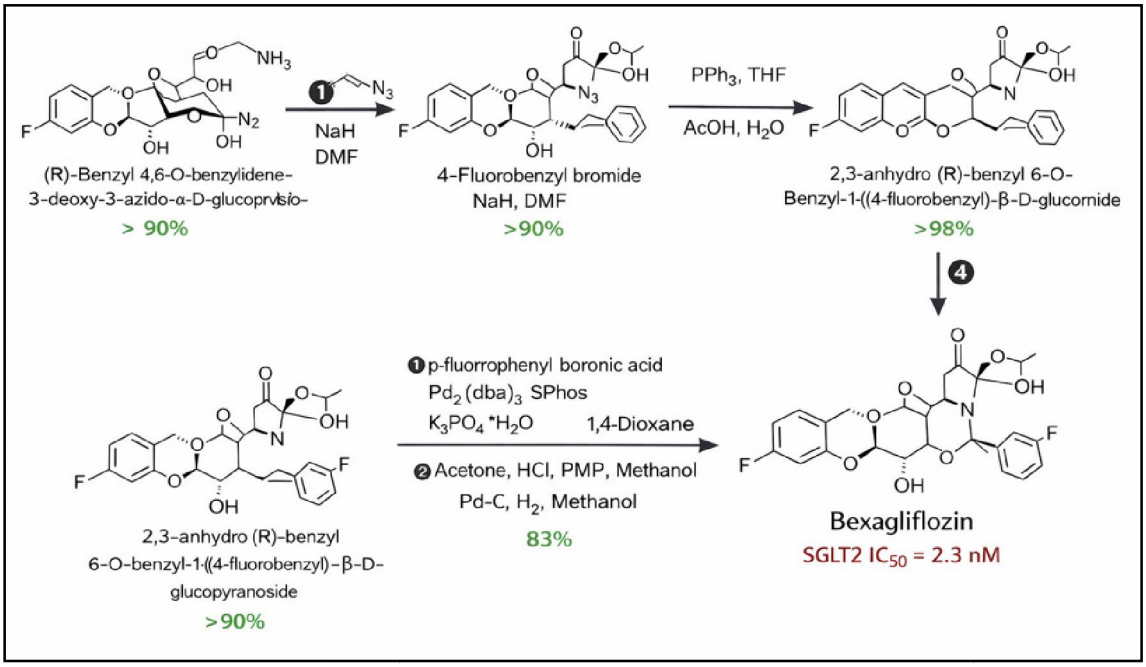

Fig. 2: The synthesis of bexagliflozin as outlined in Patent US7838499B2

Mechanistic binding of bexagliflozin

Understanding glucose reabsorption in the kidney is central to the mechanism of action of SGLT2 inhibitors. After oral administration, SGLT2 inhibitors are rapidly absorbed into the bloodstream and subsequently filtered by the

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glomerulus. Once in the renal tubular lumen, they bind to the luminal membrane of the proximal tubule, a process that requires sodium to first occupy the SGLT2 transporter. By mimicking the natural glucose reabsorption process, these inhibitors block glucose uptake, leading to increased urinary glucose excretion. This mechanism is unique to this drug class and relies on renal filtration to deliver the inhibitor to its site of action. [35]

All SGLT2 inhibitors share a similar glycone–aglycone structure, resulting in largely conserved binding interactions within the transporter. Structural studies, including models of vSGLT, have provided detailed insight into these interactions. The glycone moiety binds tightly to the glucose-binding pocket of SGLT2, stacking with the aromatic side chain of Y290 at the inner gate. Its hydroxyl groups form hydrogen bonds with surrounding residues, including N75, H80, E99, S287, W291, K321, and Q457, as well as the backbone carbonyl of F98. The amino acids involved in glucose binding are conserved between SGLT1 and SGLT2, and their functional significance has been confirmed through cysteine mutant studies. Molecular docking and modeling studies have further mapped the inhibitor binding sites within SGLT1 and SGLT2. [36]

Bexagliflozin's functional activity was first examined in vitro using a sodium-dependent methyl-α-glucopyranoside (AMG) uptake assay in cells expressing recombinant human SGLT2. The compound inhibited AMG uptake in a dose-dependent manner, confirming its potent SGLT2 activity. In vivo studies in rats and dogs supported these findings: after oral administration and subsequent glucose challenge, bexagliflozin significantly lowered blood glucose levels and increased urinary glucose excretion. Notably, rats displayed a more pronounced glucose-lowering effect, while glucosuria was observed prominently in both species. [37]

Comparisons with other SGLT2 inhibitors provide insight into structure–activity relationships. Dapagliflozin binds to the glucose site via its glycone moiety, with the aglycone oriented toward the outer vestibule, lying deeper in the binding pocket than phlorizin. Variations in glycone and aglycone moieties influence selectivity: for example, both dapagliflozin and bexagliflozin possess a hydroxyl group at carbon 6 of the glycone moiety, whereas sotagliflozin contains a sulfide at carbon 5, enabling dual inhibition of SGLT1 and SGLT2 due to stronger hydrophobic interactions in the smaller SGLT1 pocket. [38]

SGLT2 inhibitors act as competitive inhibitors with high affinity for the transporter but are only active from the extracellular surface when sodium is bound. Inhibition is reversible, though the off-rate is slower due to strong interactions between the aglycone moiety and the transporter vestibule. Upon binding, the glycone moiety occupies the glucose pocket and locks SGLT2 in an outward-facing conformation, preventing glucose reabsorption. [39]

Molecular docking studies using the Molecular Operating Environment (MOE, Amarel Desktop v.2022.02) identified the most probable binding conformation of bexagliflozin within the SGLT2 receptor. As anticipated, the glycone moiety inserts into the glucose-binding site, forming hydrogen bonds with key amino acid residues and interacting with surrounding water molecules. Figures 4a–c illustrate these interactions and the predicted conformation of bexagliflozin (shown in green) in the SGLT2 binding pocket. [40]

Metabolism

Zhang et al. investigated the metabolism of bexagliflozin through a combination of in vitro and in vivo studies in humans and animal models. Using high-performance liquid chromatography coupled with mass spectrometry (HPLC-MS), they identified the primary metabolic pathways of bexagliflozin, which include glucuronidation and oxidation. Recombinant enzyme studies further revealed that the major enzymes responsible for its metabolism are CYP3A4 and UDP-glucuronosyltransferase 1A9 (UGT1A9). Across species, metabolite 25 was consistently identified as the predominant metabolite. [41]

To determine whether these metabolites retained pharmacological activity, the authors measured sodium-dependent uptake of methyl-α-glucopyranoside (AMG) in cells expressing recombinant human SGLT2. All six primary metabolites three formed via glucuronidation and three via oxidation—exhibited less than 10% of the SGLT2 inhibitory activity of the parent compound, indicating minimal contribution to glucose-lowering effects in vivo. One exception, metabolite, showed moderate activity with an IC50 of 17.9 nM; however, its circulating concentration is too low to be clinically significant. [42]

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Excretion studies demonstrated that bexagliflozin and its metabolites are eliminated via urine, feces, and bile. The major urinary metabolite is EGT0002149 (metabolite 29), a 3-O-glucuronide formed by UGT1A9, which is highly expressed in the kidneys. This metabolite is transported via organic anion transporters and reaches plasma concentrations approaching that of the parent drug, with Cmax values of 0.243 ng/L for the metabolite and 0.727 ng/L for bexagliflozin. [43]

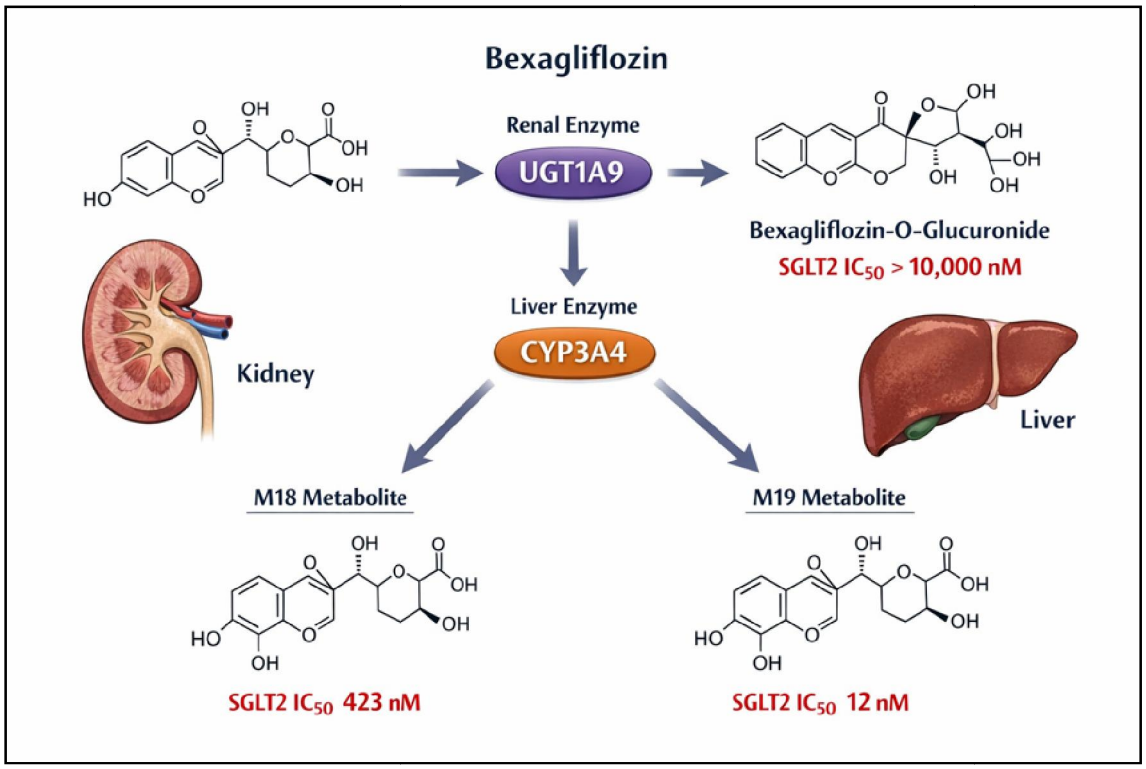

Fig 3: Metabolism of Bexagliflozin

The remaining three primary metabolites are generated through CYP3A4-mediated oxidation. These oxidative metabolites circulate at low concentrations, are minimally potent, and are primarily excreted in the feces along with the parent compound. Specifically, metabolite 27 ((S)-EGT0001663) exhibits a sevenfold higher IC50 compared with bexagliflozin but only reaches a Cmax of 0.0149 ng/L, while EGT0001494 (metabolite 25) shows a 40-fold IC50 increase with a Cmax of 0.0298 ng/L. Other metabolites demonstrate IC50 values that are 100–1000 times higher than the parent compound, with correspondingly low plasma concentrations (Cmax 0.00525–0.0368 ng/L). [44]

Overall, these findings indicate that bexagliflozin metabolites are largely inactive and present at low circulating levels, confirming that the parent compound is responsible for the majority of the drug's pharmacological effects.

Mechanism of action: pharmacology

SGLT2 inhibitors target a key physiological process in renal glucose handling. Under normal conditions, the kidneys filter large quantities of glucose, more than 85% of which is reabsorbed in the proximal tubules through the sodium–glucose cotransporter 2 (SGLT2) located on the apical membrane. In T2DM, SGLT2 expression is upregulated, resulting in excessive glucose reabsorption and persistent hyperglycemia. By selectively inhibiting SGLT2, these agents reduce renal glucose reabsorption by as much as half of the filtered load, promoting glucosuria and lowering circulating glucose concentrations. Because this pathway is independent of pancreatic β-cell insulin secretion, SGLT2

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inhibitors offer a therapeutic alternative for patients with reduced insulin production or β-cell function, including those with longstanding or advanced T2DM. [45]

Bexagliflozin, initially designated EGT1442 during development by Theracos, Inc., represents a highly potent member of this class. Chemically, it belongs to the benzyl-benzene C-glycoside family, with a molecular formula of C24H29ClO7 and a molecular weight of 464.94 g/mol. Bexagliflozin demonstrates strong inhibitory activity against SGLT2, with an inhibitory constant of 2 nmol/L, and exhibits approximately 2,400-fold selectivity for SGLT2 over SGLT1, a characteristic that enhances its renal specificity and reduces gastrointestinal off-target effects associated with SGLT1 inhibition. In healthy individuals and patients with T2DM, single and repeated dosing of bexagliflozin produces dose-dependent increases in urinary glucose excretion and urine volume, with a 20 mg once-daily dose achieving near-maximal urinary glucose excretion. Bexagliflozin is rapidly absorbed following oral administration, reaching peak plasma levels at approximately two hours, and has an apparent terminal half-life of around 12 hours, supporting its once-daily dosing regimen. The drug is primarily metabolized through UGT1A9-mediated glucuronidation—an enzyme expressed preferentially in the kidneys—and to a lesser degree via CYP3A metabolism to form its major circulating metabolite, 3′ -O-glucuronide. [46, 47]

Clinical data supporting approval: efficacy data

The clinical development program for bexagliflozin included more than 23 trials and over 5,000 adults with type 2 diabetes (T2D), providing a comprehensive evaluation of its glycemic efficacy, metabolic effects, and cardiovascular safety. Collectively, these studies show that bexagliflozin 20 mg once daily reliably improves glycemic control across a broad range of patient populations, including treatment-naïve individuals, patients inadequately controlled with oral antidiabetic therapies, and those with comorbid chronic kidney disease (CKD) or cardiovascular disease (CVD) risk factors. [48]

Early dose-finding and phase II monotherapy studies consistently demonstrated a dose-dependent reduction in HbA1c, with the 20 mg dose achieving the most robust effects. Across these studies, reductions in HbA1c typically ranged from approximately 0.5% to 0.8% versus placebo after 12–24 weeks of treatment. Parallel improvements in fasting plasma glucose were observed, alongside modest but clinically meaningful reductions in body weight. These metabolic benefits were further supported by small decreases in systolic and diastolic blood pressure, a pattern consistent with the broader SGLT-2 inhibitor class. [49]

The larger phase III trials reaffirmed these findings in more diverse and clinically representative populations. When used as monotherapy, bexagliflozin 20 mg produced superior glycemic control compared with placebo at 24 weeks, with reductions in HbA1c and fasting glucose accompanied by small decreases in body weight and systolic blood pressure. Notably, these improvements were observed in participants with baseline HbA1c values up to 10.5%, highlighting its effectiveness across a wide spectrum of hyperglycemia. [50]

Combination therapy studies demonstrated that bexagliflozin is also effective when added to metformin. In head-to-head comparisons, bexagliflozin plus metformin was shown to be noninferior to glimepiride plus metformin and to sitagliptin plus metformin, with glycemic reductions of a similar magnitude across treatment arms. Importantly, compared with glimepiride, bexagliflozin produced comparable HbA1c reductions while providing additional benefits in terms of weight loss, blood pressure reduction, and modest improvement in estimated glomerular filtration rate (eGFR). These findings suggest a broader cardiometabolic benefit profile that aligns with the mechanism of SGLT-2 inhibition. [51]

Patients with CKD stage 3a or 3b also experienced glycemic improvements with bexagliflozin, despite the attenuated efficacy typical of SGLT-2 inhibitors in reduced renal function. In this population, reductions in HbA1c and fasting glucose were accompanied by improvements in secondary markers, including reductions in systolic blood pressure, body weight, and albuminuria, suggesting potential renal protective effects that merit further study. [52]

Cardiovascular outcomes were evaluated in a dedicated phase III trial involving individuals with established CVD or multiple CVD risk factors. While bexagliflozin did not demonstrate superiority over placebo for major adverse

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cardiovascular events (MACE) or hospitalization for heart failure, it met the criterion for cardiovascular safety. Event rates were directionally favorable, with numerically fewer cases of cardiovascular death, nonfatal myocardial infarction, and heart failure hospitalization in the bexagliflozin arm, although these differences did not reach statistical significance. The overall pattern is consistent with cardiovascular neutrality rather than clear benefit, underscoring the need for additional large-scale outcome trials. [53]

Two recent meta-analyses further contextualize these findings. Pooled data from five trials showed no increased risk of MACE with bexagliflozin and confirmed significant reductions in systolic and diastolic blood pressure. A larger meta-analysis including more than 3,000 individuals demonstrated consistent reductions in HbA1c, fasting glucose, body weight, and blood pressure, and almost doubled the likelihood of achieving HbA1c <7% compared with control therapy. These analyses reinforce the robustness of the glucose-lowering and metabolic effects of bexagliflozin across patient subgroups. [54]

Finally, an ongoing head-to-head comparison between bexagliflozin and dapagliflozin will provide important comparative-effectiveness data within the SGLT-2 inhibitor class. The results are anticipated to clarify the degree to which bexagliflozin's clinical profile aligns with or diverges from that of established agents.

Taken together, the available evidence indicates that bexagliflozin is an effective and well-tolerated SGLT-2 inhibitor that provides consistent glycemic, weight, and blood pressure benefits across diverse T2D populations. While its cardiovascular effects appear neutral at present, its metabolic profile and safety signal position it as a useful therapeutic option, particularly for patients in whom weight reduction, modest blood pressure improvement, and insulin-independent glucose lowering are desirable. Additional long-term and head-to-head studies will further refine its role in contemporary diabetes management. [55]

Adverse events: safety data

Overall, oral bexagliflozin 20 mg once daily, used either as monotherapy or in combination with other antihyperglycemic agents, was generally well tolerated in individuals with type 2 diabetes (T2D) across clinical trial programs. The side-effect profile was similar to placebo or active comparators, with increased urination, genital mycotic infections, urinary tract infections, and symptoms related to mild volume depletion being among the most commonly reported events. These adverse effects are broadly consistent with other sodium-glucose co-transporter 2 (SGLT2) inhibitors and reflect the class mechanism of action, which promotes glycosuria leading to osmotic diuresis. In line with this, mild volume depletion was associated with polyuria, dehydration, dizziness, vertigo, presyncope, thirst, and occasionally orthostatic hypotension. Additional expected pharmacological effects included modest weight loss, reductions in systolic blood pressure, and transient elevations in serum creatinine. [56]

A pooled analysis of three clinical studies found that the most frequent adverse effects with bexagliflozin included increased urination (7% vs 3% with placebo), urinary tract infection (6% vs 4%), female genital mycotic infections (6% vs 0%), male genital mycotic infections (2% vs 1%), thirst (3% vs 2%), vaginal pruritus (3% vs 0%), and hypoglycemia (2% vs 1%). Data from the BEST trial in individuals with T2D at elevated cardiovascular risk demonstrated a similar overall safety profile to previous studies. [57]

Ketoacidosis, a serious and potentially life-threatening complication requiring emergency care, has been reported with SGLT2 inhibitors, including bexagliflozin. Patients taking bexagliflozin who present with signs or symptoms of dehydration or metabolic acidosis—such as nausea, vomiting, abdominal pain, malaise, or dyspnea should be evaluated for ketoacidosis even if blood glucose levels are <250 mg/dL, as euglycemic presentations have been documented.

In the BEST trial, major fractures (including hip or femur fractures) occurred at a rate of 5.4 vs 1.4 events per 1,000 patient-years in the bexagliflozin plus metformin and placebo plus metformin groups, respectively. This imbalance emerged within the first 24 weeks of treatment and persisted throughout the study. Non-traumatic lower limb amputation events occurred in both treatment groups in similar proportions, without statistically significant differences (8.3 vs 5.1 per 1,000 patient-years; HR 1.64; 95% CI 0.70–3.82).

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A recent meta-analysis reported no significant differences between bexagliflozin and placebo in the incidence of hypoglycemia (OR 0.95; p=0.60), genital mycotic infections (OR 3.11; p=0.08), urinary tract infections (OR 1.04; p=0.75), polyuria (OR 1.57; p=0.17), diabetic ketoacidosis (OR 0.44; p=0.66), or all-cause mortality (OR 0.76; p=0.28). As seen with other SGLT2 inhibitors, hypoglycemia was rare unless administered alongside insulin or sulfonylureas, reflecting preservation of SGLT1-mediated glucose absorption, reduced insulin secretion, and increased glucagon levels associated with the drug class. [58]

Comparison with other sodium-glucose cotransporter-2 inhibitors

The findings of our review align with a recent meta-analysis examining the efficacy and safety of bexagliflozin. Collectively, the available evidence indicates that bexagliflozin contributes meaningfully to glycemic control, consistent with prior research on other widely prescribed SGLT2 inhibitors. To date, all SGLT2 inhibitors have demonstrated similar reductions in HbA1c among patients with T2D. For example, an analysis by Shyangdan et al. found that patients treated with SGLT2 inhibitors were more likely to achieve an HbA1c level below 7% compared with placebo-treated patients. Likewise, a meta-analysis comparing canagliflozin, dapagliflozin, or empagliflozin against placebo demonstrated significant reductions in both HbA1c and fasting plasma glucose. SGLT2 inhibitors have also been consistently associated with decreases in body weight and systolic blood pressure. Our evaluation suggests that these metabolic and hemodynamic benefits extend to bexagliflozin, reinforcing its relevance within the drug class.

Type 2 diabetes is a well-established risk factor for atherosclerotic cardiovascular disease and heart failure. Numerous studies have shown that SGLT2 inhibitors improve cardiovascular outcomes in this population, particularly by reducing heart failure events. For instance, the EMPA-REG OUTCOME trial demonstrated that empagliflozin reduced cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke, and all-cause mortality in high-risk individuals with T2D. Similar benefits were observed in the CANVAS program with canagliflozin. In contrast, current evidence for bexagliflozin is limited. A recent meta-analysis reported only two major adverse cardiovascular events (MACEs) among patients treated with bexagliflozin, with no difference in all-cause mortality compared with placebo. Another smaller meta-analysis evaluating cardiovascular safety likewise found no significant difference in MACEs between bexagliflozin and placebo. However, these findings should be interpreted with caution, as the number of patients exposed to bexagliflozin is substantially smaller than those included in EMPA-REG and CANVAS, limiting statistical power. [59]

Adverse events associated with SGLT2 inhibitors include hypoglycemia, genital and urinary tract infections, genital fungal infections, hypersensitivity reactions, reduced intravascular volume, dysuria, and diabetic ketoacidosis. Bexagliflozin demonstrated a favorable safety profile, with minimal adverse effects and low rates of hypoglycemia across studies. Meta-analyses of empagliflozin and dapagliflozin similarly showed no significant increase in hypoglycemia risk. Nevertheless, some studies suggest a higher risk of hypoglycemia with certain SGLT2 inhibitors compared with bexagliflozin. Genital fungal infections and lower-limb amputations have been highlighted as potential safety concerns within this class. For example, the CANVAS trial reported an increased risk of amputation with canagliflozin. However, a separate meta-analysis evaluating SGLT2 inhibitors did not confirm a class-wide association with amputation risk. More recent evidence indicates that bexagliflozin and placebo do not significantly differ in this outcome.

It is important to note that direct comparative evidence between bexagliflozin and other commercially available SGLT2 inhibitors is currently lacking. No randomized controlled trial has compared bexagliflozin head-to-head against another SGLT2 inhibitor in patients with T2D. Therefore, whether bexagliflozin offers superior, inferior, or equivalent clinical value remains undetermined. Furthermore, future studies assessing cost-effectiveness will be valuable for determining how bexagliflozin fits into real-world treatment algorithms. Based on current data, bexagliflozin appears to be a safe and effective therapeutic option for T2D; however, robust comparative evidence supporting preferential use over other SGLT2 inhibitors is not yet available. Additional research is required to clarify its clinical positioning. [60]

Pharmacokinetics and pharmacodynamics of bexagliflozin in humans

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Bexagliflozin increases urinary glucose excretion and urine volume in a dose-dependent manner, reflecting its mechanism as an SGLT2 inhibitor. The recommended oral dose of 20 mg once daily has been shown to maintain therapeutic plasma concentrations with repeated administration.

Bexagliflozin is effective in patients with normal renal function as well as those with moderately impaired renal function, including CKD stages 3a and 3b, though its glucose-lowering efficacy diminishes as renal function declines.

In terms of pharmacokinetics, bexagliflozin exhibits properties comparable to other SGLT2 inhibitors. Clinical trials report an oral bioavailability of approximately 78% and a half-life of around 12 hours, supporting once-daily dosing. Two human studies measured a total clearance of 19.1 L/h, with 28.7% of the parent compound excreted in feces and 1.5% via the urine. When including metabolites, total excretion is 51.1% fecal and 40.5% renal.

Following oral administration in a fasted state, bexagliflozin reaches maximum plasma concentration (Tmax) between 2 and 4 hours. In the fed state, Tmax is delayed to approximately 5 hours, with a 31% increase in peak plasma concentration.

Bexagliflozin is slightly soluble in water and exhibits minimal hygroscopicity. It is highly protein-bound (93%) and has a large volume of distribution (262 L), indicating extensive tissue penetration. For comparison, dapagliflozin has slightly lower protein binding (91%) and a smaller volume of distribution (118 L).

Overall, these pharmacokinetic and pharmacodynamic characteristics support bexagliflozin's once-daily oral dosing, predictable systemic exposure, and consistent glucose-lowering effect across a range of patients. [61]

II. CONCLUSION

Bexagliflozin is a potent and highly selective SGLT2 inhibitor that improves glycemic control, lowers body weight and blood pressure, and is generally well tolerated in adults with type 2 diabetes. Its insulin-independent mechanism, favorable pharmacokinetics, and primarily renal metabolism support convenient once-daily dosing. Emerging data suggest preserved efficacy in moderate CKD and a cardiovascular safety profile consistent with the SGLT2 class, although definitive cardioprotective benefits have not yet been established. While bexagliflozin offers a cost-effective therapeutic alternative within the class, head-to-head trials and long-term outcome studies are needed to clarify its comparative advantages and optimal role in diabetes management.

CONFLICT OF INTEREST-

The authors hereby want to declare that there is no conflict of interest.

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