Therapeutic Class Overview
Sodium-Glucose Cotransporter 2 Inhibitors

INTRODUCTION

- Diabetes mellitus affects more than 30 million people in the United States *(Centers for Disease Control and Prevention [CDC] 2017)*.
- Type 2 diabetes mellitus (T2DM) is the most common form of diabetes and is characterized by elevated fasting and postprandial glucose concentrations *(American Diabetes Association [ADA] 2017[a])*. It is a chronic illness that requires continuing medical care and ongoing patient self-management education and support to prevent acute complications and to reduce the risk of long-term complications *(ADA 2017[b])*.
- Complications of T2DM include hypertension, heart disease, stroke, vision loss, kidney disease, and neuropathy. It is the leading cause of kidney failure and the seventh leading cause of death in the U.S. *(National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK] 2017, CDC 2017)*.
- In addition to dietary and lifestyle management, T2DM can be treated with insulin, one or more oral medications, or a combination of both. Many patients with T2DM will require combination therapy *(Garber et al 2017)*.
- Classes of oral medications for the management of blood glucose levels in patients with T2DM focus on increasing insulin secretion, increasing insulin responsiveness, or both, decreasing the rate of carbohydrate absorption, decreasing rate of hepatic glucose production, decreasing rate of glucagon secretion, and blocking glucose reabsorption by the kidney *(Garber et al 2017, Inzucchi et al 2015)*.
- Pharmacologic options for T2DM include sulfonylureas (SFUs), biguanides, thiazolidinediones (TZDs), meglitinides, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogs, amylinomimetics, sodium-glucose cotransporter 2 (SGLT2) inhibitors, combination products, and insulin.
- The SGLT2 inhibitor class consists of three agents, canagliflozin, dapagliflozin, and empagliflozin, and their combination products.
- Medispan class: Sodium-glucose cotransporter 2 inhibitors

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Dapagliflozin products	
Farxiga (dapagliflozin)	-
Xigduo XR (dapagliflozin/metformin hydrochloride extended-release)	-
Qtern (dapagliflozin/saxagliptin)	-
Canagliflozin products	
Invokana (canagliflozin)	-
Invokamet (canagliflozin/metformin hydrochloride)	-
Invokamet XR (canagliflozin/metformin extended-release)	-
Empagliflozin products	
Jardiance (empagliflozin)	-
Glyxambi (empagliflozin/linagliptin)	-
Synjardy (empagliflozin/metformin)	-
Synjardy XR (empagliflozin/metformin extended-release)	-

(*Drugs@FDA 2017, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2017*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indications	Single Entity Products			Combination Products				
	Farxiga (dapagliflozin)	Invokana (canagliflozin)	Jardiance (empagliflozin)	Glyxambi (empagliflozin/ linagliptin)	Qtern (dapagliflozin/ saxagliptin)	Invokamet, Invokamet XR† (canagliflozin/ metformin)	Synjardy, Synjardy XR† (empagliflozin/ metformin)	Xigduo XR† (dapagliflozin/ metformin ER)
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM	✓	✓	✓					
To reduce the risk of cardiovascular (CV) death in adult patients with T2DM and established CV disease			✓					
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both canagliflozin/dapagliflozin/empagliflozin and metformin is appropriate.						✓	✓*	✓
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both empagliflozin and linagliptin is appropriate				✓*				
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM who have inadequate control with dapagliflozin or who are already treated with dapagliflozin and saxagliptin					✓			

† These combination products contain metformin extended-release (ER).
* Products containing empagliflozin include the clinical trial information on EMPA-REG OUTCOME study as well as the following statement in the indications section: The effectiveness of Glyxambi/Synjardy/Synjardy XR on reducing the risk of CV death in adults with T2DM and CV disease has not been established.

Limitations of use: Canagliflozin, dapagliflozin, and empagliflozin are not recommended in patients with type 1 diabetes mellitus (T1DM) or for the treatment of diabetic ketoacidosis (DKA). Glyxambi has not been studied in patients with a history of pancreatitis. Qtern should only be used in patients who tolerate 10 mg dapagliflozin.

(*Prescribing information: Farxiga 2017, Glyxambi 2017, Invokana 2017, Invokamet 2017, Invokamet XR 2017, Jardiance 2016, Qtern 2017, Synjardy 2016, Synjardy XR 2016, Xigduo XR 2017*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- The safety and efficacy of the SGLT2 inhibitors were evaluated in patients that were drug-naïve or in patients whose glucose was inadequately controlled with other oral agents and/or insulin. SGLT2 inhibitors have demonstrated efficacy in lowering glycosylated hemoglobin (HbA1c) levels by ~0.5% to 1% *(Inzucchi et al 2015)*. They have been studied as monotherapy and in combination with other antidiabetic agents. Most trials evaluated the addition of an SGLT2 inhibitor to one or more classes of antidiabetic agents.
- The SGLT2 inhibitors have consistently shown significant beneficial effects on HbA1c, fasting plasma glucose (FPG), weight gain, post-prandial glucose (PPG), and blood pressure when used as monotherapy or in combination therapy:
  - As monotherapy *(Bailey et al 2012, Ferrannini et al 2010, Ferrannini et al 2013, Inagaki et al 2014, Stenlöf et al 2013)*
  - With metformin *(Bailey et al 2010, Haring et al 2014, Henry et al 2012, Leiter et al 2015, Rosenstock et al 2013, Rosenstock et al 2016, Ross et al 2015)*
  - With an SFU *(Fulcher et al 2015, Strojek et al 2011, Strojek et al 2014, Wilding et al 2013)*
  - With metformin and an SFU *(Haring et al 2013, Matthaei et al 2015)*
  - As add-on therapy to TZDs *(Forst et al 2014, Kovacs et al 2014, Rosenstock et al 2012)*
  - As add-on therapy or compared to DPP-4 inhibitors *(Jabbour et al 2014, Lavalle-Gonzalez et al 2013, Roden et al 2013, Rosenstock et al 2015[a], Schernthaner et al 2013)*
  - As add-on therapy to insulin *(Neal et al 2015, Rosenstock et al 2014, Rosenstock et al 2015[b], Wilding et al 2012)*
- The combination of SGLT2 inhibitors with metformin lower HbA1c compared to placebo. These studies use the coadministration of the two components instead of fixed-dose combination tablets for Invokamet, Synjardy, and Xigduo XR. The bioequivalency of Invokamet XR and Synjardy XR to the immediate release combination products in healthy subjects was used to support the Food and Drug Administration (FDA) approval of these extended-release combination products.
- Glyxambi (empagliflozin/linagliptin) was the first FDA-approved SGLT2-inhibitor/DPP-4 inhibitor combination product. A 52-week, phase 3, double-blind, parallel-group, randomized controlled trial (RCT) in patients with T2DM demonstrated reductions in HbA1c with Glyxambi that were superior to those of empagliflozin or linagliptin alone as add-on to metformin *(DeFronzo et al 2015)*. Qtern (dapagliflozin/saxagliptin) was approved in February 2017; efficacy and safety were observed as add-on therapy with saxagliptin in patients on dapagliflozin plus metformin at 24 weeks *(Matthaei et al 2015)* and at 52 weeks *(Matthaei et al 2016)*; with dapagliflozin added to saxagliptin plus metformin at 24 weeks *(Mathieu et al 2015)* and 52 weeks *(Mathieu et al 2016)*; and with saxagliptin plus dapagliflozin addition vs. the single addition of saxagliptin or dapagliflozin to metformin at 24 weeks *(Rosenstock et al 2015[a])*.
- The SGLT2 inhibitors have also shown noninferiority in decreasing HbA1c in direct comparisons when compared to SFUs:
  - Dapagliflozin vs. glipizide, both in combination with metformin *(Nauck et al 2011)*
  - Canagliflozin vs. glimepiride *(Cefalu et al 2013)*
  - Empagliflozin vs. glimepiride *(Ridderstrale et al 2014)*
- Additional studies have demonstrated the safety and efficacy of SGLT2 inhibitors in special populations:
  - Patients with T2DM and chronic kidney disease *(Barnett et al 2014, Kohan et al 2014, Yale et al 2014, Yale et al 2013)*
  - Patients with T2DM and CV disease *(Leiter et al 2014)*
  - Elderly patients *(Bode et al 1995, Bode et al 2015, Sinclair et al 2014, Sinclair et al 2016)*
    - A pooled analysis of six phase 3, double-blind, placebo-controlled, RCTs compared the efficacy and safety of canagliflozin in patients < 75 years and ≥ 75 years of age. Canagliflozin 100 mg and 300 mg were associated with placebo-subtracted mean reductions in HbA1c in patients < 75 years (-0.69% and -0.85%, respectively) and ≥ 75 years (-0.65% and -0.55%, respectively). Dose-related reductions in FPG, body weight, and blood pressure were also seen with canagliflozin 100 mg and 300 mg in patients in both age groups. Overall adverse event incidences were 67.1% with canagliflozin 100 mg, 68.6% with canagliflozin 300 mg, and 65.9% with non-canagliflozin (pooled group of comparators in all studies) in patients < 75 years, and 72.4%, 79.1%, and 72.3%, respectively, in patients ≥ 75 years, with a similar safety profile in both groups *(Sinclair et al 2016).*
- Various long-term studies have been conducted that provide data on the safety and efficacy after at least one year of treatment with the SGLT2 inhibitors *(Araki et al 2015, Bailey et al 2015, Bode et al 2015, Del Prato et al 2015, Kovacs et al 2015, Nauck et al 2014)*.
- Other post-hoc analyses of pooled data from RCTs have further evaluated the effects of SGLT2 inhibitors on parameters such as blood pressure, weight gain, and adverse events *(Davies et al 2015, Ptaszynska et al 2014, Weir et al 2014)*.

- Furthermore, various meta-analyses have been conducted that have demonstrated the individual efficacy of the SGLT2 inhibitors *(Liakos et al 2014, Orme et al 2014, Sun et al 2014, Yang et al 2014)*.

Comparative efficacy

- While there are no head-to-head studies comparing the efficacy and safety of the SGLT2 inhibitors, a 2016 systematic review and network meta-analysis found that canagliflozin 300 mg reduced HbA1c, FPG, and systolic blood pressure, while increasing low-density lipoprotein cholesterol (LDL-C) to a greater extent compared with other inhibitors (dapagliflozin and empagliflozin) at any dose *(Zaccardi et al 2016)*.
- Another systematic review and network meta-analysis found similar results *(Shyangdan et al 2016)*. When used as monotherapy, a greater proportion of patients achieved a HbA1c <7% on canagliflozin 300 mg than on canagliflozin 100 mg and dapagliflozin 10 mg, but there were no significant differences compared with either dose of empagliflozin. Canagliflozin 300 mg reduced HbA1c more than other SGLT-2 inhibitors, with the mean difference ranging from 0.20% to 0.64%. There were no significant differences between the SGLT2 inhibitors with respect to weight reduction.
- The Agency for Healthcare Research and Quality (AHRQ) updated its review of the diabetes medications for adults with T2DM to include the results from an additional eight studies *(Bolen et al 2016)*. Findings related to the SGLT2 inhibitors included some of the following:
  - Body weight was maintained or reduced by metformin, DPP-4 inhibitors, GLP-1 agonists, and SGLT2 inhibitors.
  - Systolic blood pressure was reduced by 3 to 5 mm Hg by SGLT2 inhibitors and GLP-1 agonists compared to metformin.
  - Some adverse events were higher with specific classes of drugs including gastrointestinal (GI) events (metformin and GLP-1 agonists) and risk of genital mycotic infection (SGLT2 inhibitors).

Cardiovascular outcomes studies

- EMPA-REG OUTCOME was the first study to demonstrate a positive benefit on CV outcomes due to glucose lowering with empagliflozin as add-on to standard of care in T2DM patients with high CV risk *(Zinman et al 2015)*. Empagliflozin significantly reduced the risk of the combined endpoint (CV death, nonfatal myocardial infarction [MI], or nonfatal stroke) by 14% vs. placebo ($p < 0.001$ for non-inferiority; $p = 0.04$ for superiority). In addition, there was a 38% reduction in CV death, 35% reduction in hospitalization for heart failure (HHF), and 32% reduction in death from any cause associated with its use; however, there were no significant between-group differences in the rates of MI or stroke. The underlying mechanism of empagliflozin and its effect on CV outcomes are not clearly understood. Recently updated guidelines acknowledge the established CV benefit with empagliflozin *(ADA 2017, Garber et al 2017)*.
  - A recently published follow-up to the EMPA-REG OUTCOME study examined the pre-specified secondary objective of the effect of empagliflozin on microvascular outcomes, and in particular, progression of kidney disease in patients with T2DM at high risk for CV events. In this new analysis, incident or worsening nephropathy occurred in 525 of 4124 patients taking empagliflozin and 388 of 2061 in the placebo group (12.7% vs. 18.8%; hazard ratio [HR]: 0.61; 95% confidence interval [CI], 0.53 to 0.70; $p < 0.001$). This renal end point consisted of a combination of progression to macroalbuminuria, a doubling of serum creatinine, the start of renal-replacement therapy, or renal death. A relative risk reduction of 38% was seen with the endpoint of progression to macroalbuminuria, which occurred in 459 of 4091 patients taking empagliflozin compared with 330 of 2033 patients on placebo (11.2% vs.16.2%; HR: 0.62; 95% CI, 0.54 to 0.72; $p < 0.001$) *(Wanner et al 2016)*.
- The CANVAS Program was comprised of 2 trials, the Canagliflozin Cardiovascular Assessment Study (CANVAS) and CANVAS-Renal (CANVAS-R), that included a total of 10,142 patients with T2DM and high CV risk *(Neal et al 2017)*. The studies were designed to assess the CV safety and efficacy of canagliflozin, as well as to evaluate the balance between potential benefits of the drug and its associated risks (eg, genitourinary infection, DKA, fracture). Significantly fewer participants in the canagliflozin group had a primary outcome event (the composite of death from CV causes, nonfatal MI, or nonfatal stroke) vs. placebo: 26.9 vs. 31.5 participants with an event per 1000 patient-years (HR, 0.86; 95% CI, 0.75 to 0.97; $p < 0.001$ for noninferiority; $p = 0.02$ for superiority).
- A Phase 3, multicenter trial to evaluate the effect of dapagliflozin on the incidence of CV events, known as DECLARE-TIMI58, is currently underway with results expected by 2019 *(ClinicalTrials.gov)*.
- The Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors (CVD REAL) study is the first large real-world study of > 300,000 patients with T2DM, both with and without established cardiovascular disease (CVD) that evaluated outcomes of HHF and all-cause death in patients with T2DM treated with SGLT2 inhibitors vs. other glucose-lowering drugs. Data were collected from patients living in 6 countries (United States, Germany, Sweden, Norway, Denmark, and the United Kingdom) *(Kosiborod et al 2017)*. Overall, treatment with SGLT2 inhibitors

vs. other agents was associated with a 39% relative risk reduction in HHF, a 51% reduction in all-cause death, and a 46% reduction in the HHF or death composite.

CLINICAL GUIDELINES

Overview

- Several consensus guidelines recommend metformin as the optimal first-line drug, unless there are prevalent contraindications or intolerance to treatment. SGLT2 inhibitors may be prescribed as a part of subsequent dual or triple therapy, if the target is not achieved after three months at maximum tolerated doses. All guidelines emphasize individualized therapy based upon a patient's specific factors such as comorbidities, weight, risk of hypoglycemia, and duration of diabetes *(ADA 2017[b], Copeland et al 2013, Inzucchi et al 2015)*. Metformin is considered the drug of choice for children with T2DM *(Copeland et al 2013)*.

- ADA/European Association for the Study of Diabetes (EASD) - Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach *(Inzucchi et al 2015)*
  - Monotherapy: Metformin remains the optimal drug for monotherapy due to its low cost, proven safety record, weight neutrality, and possible benefits on CV outcomes.
    - In patients intolerant of, or with contraindications for, metformin, an initial drug from other classes discussed under "Dual therapy" should be considered.
  - Dual therapy: If the HbA1c target is not achieved after ~3 months with metformin monotherapy, adding one of the six treatment options below may be considered (listed order is not meant to denote any specific preference). Other drugs (eg, alpha-glucosidase inhibitors, colesevelam, bromocriptine, and pramlintide) may be tried in specific situations but are generally not favored due to modest efficacy, the frequency of administration, and/or side effects. For all patients, initiating therapy with a dual combination should be considered when HbA1c is ≥ 9% (75 mmol/mol) in order to achieve the HbA1c target more expeditiously.
    - SFU (rapid-acting secretagogues [meglitinides] may be used instead of SFUs in patients with irregular meal schedules or those who develop late postprandial hypoglycemia on an SFU).
    - TZD
    - DPP-4 inhibitor
    - SGLT2 inhibitor
    - GLP-1 receptor agonist
    - Basal insulin
  - Triple therapy: Triple therapy may be considered if the HbA1c goal is not achieved after 3 months with dual therapy. Options for triple therapy include (order is not meant to denote any specific preference):
    - Metformin + SFU + (TZD or DPP-4 inhibitor or SGLT2 inhibitor or GLP-1 receptor agonist or insulin)
    - Metformin + TZD + (SFU or DPP-4 inhibitor or SGLT2 inhibitor or GLP-1 receptor agonist or insulin)
    - Metformin + DPP-4 inhibitor + (SFU or TZD or SGLT2 inhibitor or insulin)
    - Metformin + SGLT2 inhibitor + (SFU or TZD or DPP-4 inhibitor or insulin)
    - Metformin + GLP-1 receptor agonist + (SFU or TZD or insulin)
    - Metformin + basal insulin + (TZD or DPP-4 inhibitor or SGLT2 inhibitor or GLP-1 receptor agonist)
  - Combination injectable therapy: If the HbA1c goal is not achieved after 3 months with triple therapy and the patient is (1) on oral combination, moving to injectables is recommended; (2) on GLP-1 receptor agonist therapy, adding basal insulin is recommended; (3) on optimally treated basal insulin, adding a GLP-1 receptor agonist or mealtime insulin is recommended. In refractory patients, adding a TZD or SGLT2 inhibitor may be considered.
    - Initial therapy at this stage should be considered when blood glucose is ≥ 300 to 350 mg/dL (≥ 16.7 to 19.4 mmol/L) and/or HbA1c ≥ 10 to 12% (≥ 86 to 108 mmol/mol), especially if the patient is symptomatic or if catabolic features (weight loss, ketosis) are present, in which case basal insulin + mealtime insulin is the preferred initial regimen.

- American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) -Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm *(Garber et al 2017)*
  - The choice of diabetes therapies must be individualized based on attributes specific to both patients and the medications themselves. Medication selection should consider antihyperglycemic efficacy, mechanism of action, risk of inducing hypoglycemia, risk of weight gain, other adverse events, tolerability, ease of use, likely adherence, cost,

and safety in heart, kidney, or liver disease. Minimizing the risks of hypoglycemia and weight gain are priorities. These guidelines recommend the following therapies:

- Lifestyle therapy, including a medically assisted weight loss program, is recommended for all patients.
- Should patients not achieve their goal HbA1c in three months, it is recommended that they escalate and add on therapy (medication options listed in order of recommended choice):

For HbA1c of < 7.5%:

- Monotherapy: Metformin, a GLP-1 receptor agonist, SGLT2 inhibitor, DPP-4 inhibitor, or an alpha-glucosidase inhibitor. TZD or SFU/glinide should be used with caution.

For HbA1c of ≥ 7.5%:

- Dual therapy: Metformin or another first-line agent + a second agent (eg, GLP-1 receptor agonist, SGLT2 inhibitor, DPP-4 inhibitor, colesevelam, bromocriptine quick release [QR], or an alpha-glucosidase inhibitor). TZD, basal insulin, or SFU/glinide should be used with caution.
- Triple therapy: Metformin or another first-line agent + a second-line agent + a third agent (eg, GLP-1 receptor agonist, SGLT2 inhibitor, DPP-4 inhibitor, colesevelam, bromocriptine QR, or an alpha-glucosidase inhibitor). TZD, basal insulin, or SFU/glinide should be used with caution.
- If triple therapy fails to achieve the HbA1c goal in three months, then adding or intensifying insulin therapy should be considered.

For HbA1c of > 9%:

- In patients without symptoms, dual therapy or triple therapy should be considered.
- In patients with symptoms, insulin ± other agents should be considered.
- For patients with or without symptoms, adding or intensifying insulin should be considered.

SGLT2 inhibitor-specific information:

- SGLT2 inhibitors have a glucosuric effect that results in decreased HbA1c, weight, and systolic blood pressure.
- Empagliflozin is the only SGLT2 inhibitor associated with significantly lower rates of all-cause and CV death and lower risk of HHF. Empagliflozin received FDA-approval for the indication of reduction of cardiac mortality.
- Safety concerns with treatment include increased risks of mycotic genital infections, slightly increased LDL-C levels, limited efficacy in patients with an estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73 m^2, potential hypotension due to increased diuresis, and incidences of bone fractures in patients taking canagliflozin and dapagliflozin. Post-marketing reports of DKA have been reported in T1DM and T2DM with less than expected hyperglycemia (euglycemic DKA).

- ADA Standards of Medical Care in Diabetes – 2017 *(ADA 2017[b])*
  - A patient-centered approach should be used to guide the choice of pharmacologic agents. Considerations include efficacy, hypoglycemia risk, impact on weight, potential side effects, cost, and patient preferences. Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacologic agent for the treatment of T2DM.
  - SGLT2 inhibitors provide insulin-independent glucose lowering by blocking glucose reabsorption in the proximal renal tubule by inhibiting SGLT2. These agents provide modest weight loss and blood pressure reduction in T2DM. None of the available 3 agents are FDA-approved for the treatment of patients with T1DM.
  - The FDA issued a warning about the risk of ketoacidosis occurring in the absence of significant hyperglycemia (euglycemic DKA) in patients with type 1 and type 2 diabetes treated with SGLT2 inhibitors. Symptoms of ketoacidosis include dyspnea, nausea, vomiting, and abdominal pain. Patients should be instructed to stop taking SGLT2 inhibitors and seek medical attention immediately if they have symptoms or signs of ketoacidosis.
  - In patients with long-standing suboptimally controlled T2DM and established atherosclerotic CV disease, empagliflozin or liraglutide should be considered as they have been shown to reduce CV and all-cause mortality when added to standard care.

SAFETY SUMMARY

- Contraindications:
  - History of serious hypersensitivity reaction to canagliflozin, dapagliflozin, or empagliflozin.
  - Severe renal impairment (eGFR < 30 mL/min/1.73 m^2), end-stage renal disease, or dialysis.
  - Metformin-containing products have the following contraindications:
    - Severe renal impairment (Invokamet, Invokamet XR, Synjardy, Synjardy XR: eGFR < 45 mL/min/1.73 m^2; Xigduo XR: eGFR < 60 mL/min/1.73 m^2), end-stage renal disease, or dialysis

- Known hypersensitivity to metformin hydrochloride
- Acute or chronic metabolic acidosis, including DKA, with or without coma. DKA should be treated with insulin.

○ Linagliptin-containing products have the following contraindications:
- History of hypersensitivity reactions to linagliptin, such as anaphylaxis, angioedema, exfoliative skin conditions, urticarial, or bronchial hyperreactivity.

○ Saxagliptin-containing products have the following contraindications:
- History of a serious hypersensitivity reaction to dapagliflozin or to saxagliptin, including anaphylaxis, angioedema or exfoliative skin conditions.
- Moderate to severe renal impairment (eGFR < 45 mL/min/1.73 m^2), end-stage renal disease, or dialysis.

• Boxed Warnings:

○ Canagliflozin-containing products carry a Boxed Warning for lower limb amputation. An approximately 2-fold increased risk of lower limb amputations associated with canagliflozin use was observed in the CANVAS and CANVAS-R trials in patients with T2DM who had established CVD or were at risk for CVD. Amputations of the toe and midfoot were most frequent; however, amputations involving the leg were also observed. Some patients had multiple amputations, some involving both limbs. Before initiating, consider factors that may increase the risk of amputation. Monitor patients receiving canagliflozin for infections or ulcers of the lower limbs, and discontinue if these occur.

○ Metformin-containing products carry a Boxed Warning for lactic acidosis. Lactic acidosis can occur due to metformin accumulation. The risk increases with conditions such as concomitant use of certain drugs, age > 65 years, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment. Symptoms include malaise, myalgias, respiratory distress, increasing somnolence, and abdominal pain. Laboratory abnormalities include increased lactate/pyruvate ratio, anion gap acidosis, metformin plasma levels generally > 5 mcg/mL, and elevated blood lactate. If acidosis is suspected, discontinue treatment and hospitalize the patient immediately.

• Warnings and Precautions

○ Several FDA drug safety communications have been issued for canagliflozin over the past year.
- The FDA published a drug safety communication in June 2016 stating that the existing warning about the risk of acute kidney injury for canagliflozin (Invokana, Invokamet, Invokamet XR) and dapagliflozin (Farxiga, Xigduo XR) has been strengthened. Based on recent confirmed cases of acute kidney injury, the warning in the drug label has been revised to include more specific parameters regarding the monitoring of renal function and discontinuation in cases of renal impairment *(FDA Drug Safety Communication 2016[b])*.
- The drug safety communication issued in May 2016 with interim safety results from the CANVAS and CANVAS-R studies has since culminated in a formal boxed warning on all canagliflozin-containing agents for the risk of lower limb amputation *(FDA Drug Safety Communication 2016[a] and 2017)*.
- The FDA issued a drug safety communication regarding the risk of fracture and bone density in 2016.
  - The FDA evaluated the incidence of bone fractures based on a pooled analysis of nine clinical trials (n = 10,194) with patients ages 55 to 80 who had a mean duration of exposure to canagliflozin of 85 weeks. The incidence rates of bone fractures were greater with canagliflozin 100 mg and 300 mg vs. placebo or an active comparator (1.4 and 1.5 vs. 1.1 per 100 patient-years of exposure, respectively). Fractures were observed as early as 12 weeks after treatment initiation and were more likely to be low trauma (eg, fall from no more than standing height), and affect the upper extremities *(Watts et al 2016)*.
  - Based on an FDA-required post-marketing trial, canagliflozin caused greater loss of bone mineral density at the hip and lower spine than placebo over two years in elderly individuals (55 to 80 years of age) with poorly controlled T2DM. Placebo-corrected declines in bone mineral density at the total hip were 0.9% and 1.2%, respectively for canagliflozin 100 mg and 300 mg, and were 0.1% at the femoral neck for both canagliflozin doses. Placebo-adjusted bone mineral density decline at the distal forearm was 0.4% with canagliflozin 300 mg and 0% with canagliflozin 100 mg *(Bilezikian et al 2016, FDA Drug Safety Communication 2015)*.

Table 3. Warnings and Precautions

Warnings and Precautions	Single-Entity Products			Combination Products				
	Farxiga (dapagliflozin)	Invokana (canagliflozin)	Jardiance (empagliflozin)	Glyxambi (empagliflozin/ linagliptin)	Qtern (dapagliflozin/ saxagliptin)	Invokamet, Invokamet XR (canagliflozin/ metformin)	Synjardy, Synjardy XR (empagliflozin/ metformin)	Xigduo XR (dapagliflozin/ metformin ER)
Hypotension: Before initiating therapy, assess volume status and correct hypovolemia in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics.	✔	✔	✔	✔	✔	✔	✔	✔
Ketoacidosis: Assess patients who present with signs/symptoms of metabolic acidosis regardless of blood glucose level.	✔	✔	✔	✔	✔	✔	✔	✔
Acute kidney injury and impairment in renal function: Consider temporarily discontinuing in settings of reduced oral intake or fluid losses. If acute kidney injury occurs, discontinue and promptly treat. Monitor renal function during therapy.	✔	✔	✔	✔	✔	✔	✔	✔
Impairment in renal function: Monitor renal function during therapy. More frequent monitoring is recommended in patients with eGFR < 60 mL/min/1.73 m^2. Avoid use of dapagliflozin when eGFR < 60 mL/min/1.73 m^2.	✔	✔	✔	✔	✔	✔	✔	✔
Hypoglycemia: Consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia when used in combination.	✔	✔	✔	✔	✔	✔	✔	✔
Macrovascular outcomes: No clinical studies have established conclusive evidence of macrovascular risk reduction.	✔	✔		✔	✔	✔	✔	✔
Hyperkalemia: Monitor potassium levels in patients with impaired renal function and in patients predisposed to hyperkalemia.		✔				✔		
Hypersensitivity reactions: Monitor for anaphylaxis and angioedema. Discontinue use and treat and monitor until signs and symptoms resolve.		✔		✔	✔	✔		
Genital mycotic infections: Monitor and treat if indicated.	✔	✔	✔	✔	✔	✔	✔	✔
Increased LDL-C: Monitor LDL-C and treat per standard of care.	✔	✔	✔	✔	✔	✔	✔	✔
Bladder cancer: An imbalance in bladder cancers was observed in clinical trials. Dapagliflozin should not be used in patients with active bladder cancer and should be used with	✔				✔			✔

Warnings and Precautions	Single-Entity Products			Combination Products				
	Farxiga (dapagliflozin)	Invokana (canagliflozin)	Jardiance (empagliflozin)	Glyxambi (empagliflozin/ linagliptin)	Qtern (dapagliflozin/ saxagliptin)	Invokamet, Invokamet XR (canagliflozin/ metformin)	Synjardy, Synjardy XR (empagliflozin/ metformin)	Xigduo XR (dapagliflozin/ metformin ER)
caution in patients with a prior history of bladder cancer.								
Lower limb amputation: An approximately 2-fold increased risk of lower limb amputations was observed with canagliflozin in patients with T2DM who had either established CVD or were at risk for CVD.		✔				✔		
Urosepsis and Pyelonephritis: Evaluate for signs/symptoms of UTI and treat promptly, if indicated.	✔	✔	✔	✔	✔	✔	✔	✔
Bone fracture: An increased risk of bone fracture, occurring as early as 12 weeks after treatment initiation, was observed. Consider factors that contribute to fracture risk before initiating canagliflozin		✔				✔		
Vitamin B_{12} deficiency: Metformin may lower vitamin B_{12} levels. Monitor hematologic parameters annually.						✔	✔	✔
Pancreatitis: There have been post marketing reports of acute pancreatitis, including fatal pancreatitis. Discontinue if suspected.				✔	✔			
Arthralgia: Severe and debilitating arthralgia has been reported in patients taking DPP-4 inhibitors. Consider as a possible cause for severe joint pain and discontinue if appropriate.				✔	✔			
Bullous pemphigoid: Patients taking DPP-4 inhibitors have required hospitalization due to bullous pemphigoid. Patients should report development of blisters or erosions. Discontinue if suspected.				✔	✔			
Heart failure: In a CV outcomes trial enrolling participants with established atherosclerotic cardiovascular disease (ASCVD) or multiple risk factors for ASCVD (SAVOR trial), more patients randomized to saxagliptin (289/8280, 3.5%) were hospitalized for heart failure compared to patients randomized to placebo (228/8212, 2.8%). In a time-to-first-event analysis the risk of HHF was higher in the saxagliptin group (estimated HR: 1.27; 95% CI, 1.07 to 1.51). Subjects with a prior history of heart failure and					✔			

Warnings and Precautions	Single-Entity Products			Combination Products				
	Farxiga (dapagliflozin)	Invokana (canagliflozin)	Jardiance (empagliflozin)	Glyxambi (empagliflozin/ linagliptin)	Qtern (dapagliflozin/ saxagliptin)	Invokamet, Invokamet XR (canagliflozin/ metformin)	Synjardy, Synjardy XR (empagliflozin/ metformin)	Xigduo XR (dapagliflozin/ metformin ER)
subjects with renal impairment had a higher risk for HHF, irrespective of treatment assignment; monitor, observe, and advise patients of this risk and consider discontinuation in any patients that develop signs of heart failure.								
Radiologic studies with intravascular iodinated contrast materials: metformin can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Metformin-containing agents should be withheld at the time of or prior to the procedure (and withheld for 48 hours subsequent to the procedure). They should be reinstituted only after renal function is normal or mildly impaired.						✔	✔	✔

- Adverse effects:
  - The most common adverse effects seen with the SGLT2 inhibitors are genital mycotic infections and urinary tract infections.
  - Most common adverse reactions associated with metformin (5% or greater incidence) are diarrhea, nausea, vomiting, flatulence, asthenia, indigestion, abdominal discomfort, and headache.
- Drug Interactions:

  All SGLT2 Inhibitors:
  - Positive urine glucose test: Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.
  - Interference with 1,5-anhydroglucitol (1,5-AG) assay: Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

  Canagliflozin:
  - Co-administration of canagliflozin with inducers of uridine diphosphate glucuronosyltransferase (UGT) enzymes such as rifampin, phenytoin, phenobarbital, and ritonavir may result in decreased canagliflozin area under the concentration curve (AUC); consider increasing canagliflozin dosage to 300 mg once daily in patients tolerating 100 mg once daily who have an eGFR of 60 mL/min/1.73 m^2 or more and require additional glycemic control. Consider another antihyperglycemic agent in patients with eGFR of 45 to less than 60 mL/min/1.73 m^2 receiving concurrent therapy with a UGT inducer.
  - Co-administration of canagliflozin 300 mg with digoxin have been reported to increase the AUC and mean peak drug concentration of digoxin (20% and 36%, respectively).

  Dapagliflozin:
  - When dapagliflozin is used with insulin or an insulin secretagogue (eg, SFU), a lower dose of insulin or the insulin secretagogue may be required to reduce the risk of hypoglycemia.

  Empagliflozin:

- Diuretics: Co-administration of diuretics with increased urine volume and frequency of voids may increase the potential for volume depletion.

Linagliptin-containing products:

- Efficacy of linagliptin may be reduced when used in combination with a strong inducer of cytochrome P450 (CYP) 3A4 or P-glycoprotein. Consider alternative treatments.

Saxagliptin-containing products:

- Ketoconazole significantly increased saxagliptin exposure. Similar significant increases in plasma concentrations of saxagliptin are anticipated with other strong CYP3A4/5 inhibitors; do not co-administer Qtern with strong CYP3A4/5 inhibitors.

Metformin-containing products:

- Cationic drugs such as cimetidine may reduce metformin elimination and may increase the risk for lactic acidosis. Other drugs which may increase exposure to metformin include ranolazine, vandetanib, and dolutegravir.
- Alcohol may potentiate the effect of metformin on lactate metabolism. Advise against excessive alcohol intake.
- Topiramate or other carbonic anhydrase inhibitors (eg, zonisamide, acetazolamide, or dichlorphenamide) frequently decrease serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs may induce metabolic acidosis and may increase the risk of lactic acidosis.
- Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid. When such drugs are administered, monitor for loss of blood glucose control. When such drugs are withdrawn from a patient receiving a metformin-containing drug, monitor for hypoglycemia.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Single entity products				
Farxiga (dapagliflozin)	Tablets	Oral	Daily	Initiation is not recommended if eGFR is < 60 mL/min/1.73 m^2. Not recommended in patients with an eGFR persistently between 30 and < 60 mL/min/1.73 m^2.
Invokana (canagliflozin)	Tablets	Oral	Daily	Limit dose to 100 mg once daily in patients who have an eGFR of 45 to < 60 mL/min/1.73 m^2. Not recommended if eGFR persistently falls below 45 mL/min/1.73 m^2. Not recommended in cases of severe hepatic impairment.
Jardiance (empagliflozin)	Tablets	Oral	Daily	Do not initiate if eGFR is < 45 mL/min/1.73 m^2. Discontinue therapy if eGFR falls below 45 mL/min/1.73 m^2.
Combination products				
Invokamet (canagliflozin/ metformin)	Tablets	Oral	Two times daily	Limit canagliflozin to 50 mg twice daily in patients with eGFR of 45 to < 60 mL/min/1.73 m^2. Contraindicated in patients with moderate to severe renal impairment (eGFR < 45

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				mL/min/1.73 m^2), end stage renal disease, or patients on dialysis. Not recommended in patients with hepatic impairment.
Invokamet XR (canagliflozin/ metformin ER)	Tablets	Oral	Daily	Limit canagliflozin to 50 mg twice daily in patients with eGFR of 45 to < 60 mL/min/1.73 m^2. Contraindicated in patients with moderate to severe renal impairment (eGFR < 45 mL/min/1.73 m^2), end stage renal disease, or patients on dialysis. Not recommended in patients with hepatic impairment.
Xigduo XR (dapagliflozin/ metformin ER)	Tablets	Oral	Daily	Contraindicated in patients with moderate to severe renal impairment (eGFR < 60 mL/min/1.73 m^2). Not recommended in hepatic impairment.
Qtern (dapagliflozin/ saxagliptin)	Tablets	Oral	Daily	Do not initiate if eGFR is < 60 mL/min/1.73 m^2. Discontinue if eGFR falls persistently below 60 mL/min/1.73 m^2.
Glyxambi (empagliflozin/ linagliptin)	Tablets	Oral	Daily	Do not initiate or continue if eGFR < 45 mL/min/1.73 m^2. Discontinue if eGFR is < 45 mL/min/1.73 m^2.
Synjardy (empagliflozin/ metformin)	Tablets	Oral	Two times daily	Contraindicated in patients with eGFR < 45 mL/min/1.73 m^2. Advise premenopausal females of the potential for an unintended pregnancy.
Synjardy XR (empagliflozin/ metformin ER)	Tablets	Oral	Daily	Contraindicated in patients with eGFR < 45 mL/min/1.73 m^2. Advise premenopausal females of the potential for an unintended pregnancy.

See the current prescribing information for full details

CONCLUSION

- Canagliflozin, dapagliflozin, and empagliflozin are inhibitors of SGLT2, the co-transporter responsible for the majority of reabsorption of glucose filtered by the kidney. By inhibiting SGLT2, these agents reduce reabsorption of filtered glucose, lower the renal threshold for glucose, and thereby increase urinary glucose excretion.
- Similar to other currently available oral antidiabetic agents, SGLT2 inhibitors are indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. SGLT2 inhibitors have demonstrated efficacy in lowering HbA1c levels by ~0.5% to 1%. They have been studied as monotherapy and in combination with metformin and other antidiabetic agents.

- The SGLT2 inhibitor/metformin combinations include Invokamet/Invokamet XR (canagliflozin/metformin), Synjardy/Synjardy XR (empagliflozin/metformin), and Xigduo XR (dapagliflozin/metformin). Glyxambi (empagliflozin/linagliptin) and Qtern (dapagliflozin/saxagliptin) are SGLT2 inhibitor/DPP-4 inhibitor combination products.
- In clinical trials, the SGLT2 inhibitors have been evaluated in patients that were drug-naïve or in patients whose glucose was inadequately controlled with other oral agents and/or insulin. They have demonstrated effectiveness when used as monotherapy and in combination with other antidiabetic agents. Most trials evaluated the addition of an SGLT2 inhibitor to one or more classes of antidiabetic agents.
- The SGLT2 inhibitors have consistently shown significant beneficial effects on HbA1c, FPG, weight gain, PPG, and blood pressure when used as monotherapy or in combination therapy.
- SGLT2 inhibitors have additional beneficial effects such as weight reduction and decreases in blood pressure. These beneficial changes are hypothesized to result from either a loss of calories associated with induction of urinary glucose excretion or a reduction in fluid volume through the osmotic diuretic effect. These agents are not associated with hypoglycemia; however, hypoglycemia risk may increase when combined with insulin or an insulin secretagogue.
- All three single-entity SGLT2 inhibitors are dosed once daily. Dapagliflozin is not recommended in patients with an eGFR < 60 mL/min/1.73 m^2. Empagliflozin and canagliflozin are not recommended in patients with an eGFR < 45 mL/min/1.73 m^2. Volume depletion issues should be corrected prior to initiation of SGLT2 therapy.
- The SGLT2 inhibitors share a similar safety profile, including increased LDL-C levels, increased serum creatinine and a concomitant decrease in eGFR, volume depletion, and genital mycotic infections. Warnings for bone fractures and most recently, lower limb amputation were added for canagliflozin-containing products. Warnings for DKA, urosepsis, and pyelonephritis were also added to the labeling of SGLT2 inhibitors after increased incidences were reported post-marketing.
- Consensus guidelines generally recommend metformin as the optimal first-line drug, unless there are prevalent contraindications or intolerance to treatment. SGLT2 inhibitors may be prescribed as a part of subsequent dual or triple therapy, if the target is not achieved after three months at maximum tolerated doses. All guidelines emphasize individualized therapy based upon a patient's specific factors such as comorbidities, weight, risk of hypoglycemia, and duration of diabetes.
- Evidence that glucose lowering reduces the rates of CV events and death had not been convincingly shown until the publication of results from the EMPA-REG OUTCOME trial, which was a long-term, placebo-controlled study involving 7020 patients with T2DM at high risk for CV events. When added to standard of care, empagliflozin significantly reduced the risk of the combined endpoint (CV death, nonfatal MI, or nonfatal stroke) by 14% vs. placebo ($p < 0.001$ for non-inferiority; $p = 0.04$ for superiority). In the CANVAS trials, significantly fewer participants in the canagliflozin group had a primary outcome event (the composite of death from CV causes, nonfatal MI, or nonfatal stroke) vs. placebo: 26.9 vs. 31.5 participants with an event per 1000 patient-years (HR: 0.86; 95% CI, 0.75 to 0.97; $p < 0.001$ for noninferiority; $p = 0.02$ for superiority).
- The SGLT2 inhibitors may provide another treatment option for glycemic control in patients unable to tolerate first-line treatment with metformin or other oral antidiabetic therapies due to adverse effects or risk for hypoglycemia. Positive CV outcomes have been demonstrated with empagliflozin and now most recently with canagliflozin, which suggest that SGLT2 inhibitors may play a significant role in T2DM patients at high risk for CV events; however, the results of an ongoing CV outcomes study with dapagliflozin are still pending. Although the long term effects of SGLT2 inhibition are not known at this time, clinical studies demonstrate that the benefits outweigh the risks.

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