

Therapeutic Class Overview

Sodium-Glucose Cotransporter 2 Inhibitors

INTRODUCTION

- Diabetes mellitus affects **more than 29 million** people in the United States (Centers for Disease Control [CDC], **2016**).
- 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. (CDC, **2016**).
- 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 type 2 diabetes include sulfonylureas, 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 inhibitors 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	Manufacturer	FDA Approval Date	Generic Availability
Dapagliflozin products			
FARXIGA™ (dapagliflozin)	AstraZeneca / Bristol Myers Squibb	01/08/2014	-
XIGDUO XR™ (dapagliflozin/ metformin hydrochloride extended release)	AstraZeneca Pharmaceuticals	10/29/2014	-
Canagliflozin products			
INVOKANA™ (canagliflozin)	Janssen Pharmaceuticals	03/29/2013	-
INVOKAMET® (canagliflozin/metformin hydrochloride)	Janssen Pharmaceuticals	08/08/2014	-
INVOKAMET® XR (canagliflozin/metformin extended release)	Janssen Pharmaceuticals	09/20/2016	-
Empagliflozin products			
JARDIANCE® (empagliflozin)	Boehringer Ingelheim Pharmaceuticals / Eli Lilly & Co.	08/01/2014	-
GLYXAMBI® (empagliflozin/linagliptin)	Boehringer Ingelheim Pharmaceuticals / Eli Lilly & Co.	01/30/2015	-
SYNJARDY® (empagliflozin/metformin)	Boehringer Ingelheim Pharmaceuticals / Eli Lilly & Co.	08/26/2015	-

Drug	Manufacturer	FDA Approval Date	Generic Availability
SYNJARDY® XR (empagliflozin/metformin extended release)	Boehringer Ingelheim Pharmaceuticals / Eli Lilly & Co.	12/09/2016	-

(Drugs@FDA, 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)	INVOKAMET, INVOKAMET XR (canagliflozin/metformin)	SYNJARDY, SYNJARDY XR (empagliflozin/metformin)	XIGDUO XR (dapagliflozin/metformin XR)
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				✓*			

*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 type 2 diabetes mellitus 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. GLYXAMBI has not been studied in patients with a history of pancreatitis.

(Prescribing information: FARXIGA, 2016; GLYXAMBI, 2016; INVOKANA, 2016; INVOKAMET, 2016; INVOKAMET XR, 2016; JARDIANCE, 2016; SYNJARDY, 2016; SYNJARDY XR, 2016; XIGDUO XR, 2016)

Information on indications, mechanism of action, pharmacokinetics, 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 ~0.6% to 1%. 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 (FPB), weight gain, post-prandial glucose (PPG), and blood pressure when used as monotherapy or in combination therapy:
 - As monotherapy (Bailey et al, 2012; Inagaki et al, 2014; Ferrannini et al, 2010; Ferrannini et al, 2013; Stenlöf et al, 2013)
 - With metformin (Haring et al, 2014[a]; Henry et al, 2012; Bailey et al, 2010; Leiter et al, 2015; Rosenstock et al, 2013; Rosenstock et al, 2016; Ross et al, 2015)
 - With a sulfonylurea (Fulcher et al, 2015; Strojek et al, 2011; Strojek et al, 2014; Wilding et al, 2013)
 - With metformin and a sulfonylurea (Haring et al, 2014[b]; Matthaai et al, 2015)
 - TZDs (Kovacs et al, 2014; Rosenstock et al, 2012; Forst et al, 2012)
 - DPP-4 inhibitor (Roden et al, 2013; Jabbour et al, 2014; Lavallo-Gonzalez et al, 2013; Rosenstock et al, 2015[a]; Schernthaner et al, 2013)
 - Insulin (Rosenstock et al, 2014; Rosenstock et al, 2015[b]; Wilding et al, 2012; Neal et al, 2015).
- 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 FDA approval of these extended release combination products.
- GLYXAMBI (empagliflozin/linagliptin) is the first FDA-approved SGLT2-inhibitor/DPP-4 inhibitor combination product. A 52-week, phase 3, double-blind, parallel-group, randomized-controlled trial 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).
- The SGLT2 inhibitors have also shown noninferiority in decreasing HbA1c in direct comparisons when compared to sulfonylureas:
 - 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).
- As of yet, there are no direct comparative trials comparing the efficacy of canagliflozin, dapagliflozin, and empagliflozin.
- Additional studies have demonstrated the safety and efficacy of SGLT2 inhibitors in special populations:
 - Patients with type 2 diabetes and chronic kidney disease (Barnett et al, 2014; Kohan et al, 2014; Yale et al, 2014; Yale et al, 2013)
 - Patients with type 2 diabetes 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, randomized clinical trials 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 randomized controlled trials 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 efficacy of the SGLT2 inhibitors (Liakos et al, 2014; Orme et al, 2014; Sun et al, 2014; Yang et al, 2014).
- The Agency for Healthcare Research and Quality (AHRQ) updated the review of the diabetes medications for adults with T2DM (Bolen et al, 2016). An additional eight new studies were identified. DPP-4 inhibitors were noted to have more evidence demonstrating that the reductions in HbA1c were less than observed with metformin. Monotherapy with metformin, TZDs, and sulfonylureas reduce HbA1c to a similar degree. Body weight was maintained or reduced by metformin, DPP-4 inhibitors, GLP-1 agonists, and SGLT2 inhibitors. Weight gain was associated with sulfonylureas, TZDs, and insulin with between group differences of 1 to 5 kg. Systolic blood pressure was reduced by 3 to 5 mm Hg by SGLT2 inhibitors and GLP-1 agonists compared to metformin. Risk of total and severe hypoglycemia was increased with sulfonylureas compared to monotherapy with metformin or TZDs. 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). Moderate strength evidence supports that sulfonylurea monotherapy was associated with a 50 to 70 percent higher relative risk (absolute risk 0.1 to 2.9% in RCT; number needed to treat range 20 to 1000) of CV mortality compared with metformin monotherapy.
- 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). Whether this benefit is a class effect remains unclear; long-term studies on CV outcomes for canagliflozin and dapagliflozin are currently ongoing, with results expected in 2018 and 2019, respectively.
 - 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%; HR: 0.61; 95% 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).

Guidelines:

- 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; 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 recommend metformin as initial monotherapy for T2DM also (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 (e.g., 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 $\geq 9\%$ (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 BG 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 were recently updated from 2016 (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 $\geq 7.5\%$:

- Dual therapy: Metformin or another first-line agent + a second agent (e.g., 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 (e.g., 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 inhibitors specific information:

- SGLT2 inhibitors have a glucosuric effect that results in decreased HbA1c, weight, and SBP.
- Empagliflozin is the only SGLT2 inhibitor associated with significantly lower rates of all-cause and CV death and lower risk of hospitalization for heart failure. **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 low-density lipoprotein cholesterol (LDL-C) levels, limited efficacy in patients with an eGFR < 45 mL/min/1.73 m², potential hypotension due to increased diuresis, and incidences of bone fractures in patients taking canagliflozin and dapagliflozin. Post-marketing reports of diabetic ketoacidosis (DKA) have been reported in T1DM and T2DM with less than expected hyperglycemia (euglycemic DKA).

SAFETY SUMMARY

- Contraindications:
 - History of serious hypersensitivity reaction to canagliflozin, dapagliflozin, or empagliflozin.
 - Severe renal impairment (eGFR < 30 mL/min/1.73 m²), 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 m²; XIGDUO XR: eGFR < 60 mL/min/1.73 m²), end-stage renal disease, or dialysis.
 - Known hypersensitivity to metformin hydrochloride
 - Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis 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.
- Boxed Warnings:
 - 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 increase 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 the 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).
- The FDA issued a new drug safety communication in May 2016 with interim safety results from an ongoing clinical trial that found an increase in leg and foot amputations, mostly affecting the toes, in patients treated with canagliflozin. The FDA is currently investigating this new safety issue and will provide an update when there is more information available (FDA Drug Safety Communication, May 2016).
 - The FDA issued drug safety communication regarding the risk of fracture and bone density in 2016.
 - Bone fracture –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 (e.g., fall from no more than standing height), and affect the upper extremities (Watts et al, 2016).
 - Decreased bone mineral density – 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)	INVOKAMET, INVOKAMET XR (canagliflozin/	SYNJARDY, SYNJARDY XR (empagliflozin/	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 caution in patients with a prior history of bladder cancer.	✓						✓
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.				✓			
Radiologic studies with intravascular iodinated contrast materials: metformin can lead to acute					✓	✓	✓

<p>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 reinstated only after renal function is normal or mildly impaired.</p>								
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- 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 INVOKANA 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 m² or more and require additional glycemic control. Consider another antihyperglycemic agent in patients with eGFR of 45 or less than 60 mL/min/1.73 m² 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 (e.g., sulfonylurea) a lower dose of insulin or the insulin secretagogue may be required to reduce the risk of hypoglycemia.

Empagliflozin:

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

Linagliptin-containing agents:

- Efficacy of linagliptin may be reduced when used in combination with a strong inducer of CYP3A4 or P-gp. Consider alternative treatments.

Metformin-containing agents:

- 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.
- Carbonic anhydrase Inhibitors: Topiramate or other carbonic anhydrase inhibitors (e.g., 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.
- Drugs affecting glycemic control: 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	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Single entity products				
FARXIGA (dapagliflozin)	Tablet: 5 mg, 10 mg	Starting dose is 5 mg once daily in the morning. Dose can be increased to 10 mg once daily in patients tolerating FARXIGA who require additional glycemic control.	Assess renal function before initiating FARXIGA. Do not initiate FARXIGA if eGFR is < 60 mL/min/1.73 m ² .	Take with or without food.
INVOKANA (canagliflozin)	Tablet: 100 mg, 300 mg	The recommended starting dose is 100 mg once daily. Dose can be increased to 300 mg once daily in patients who have an eGFR ≥ 60 mL/min/1.73 m ² and require additional glycemic control.	Limit dose to 100 mg once daily in patients who have an eGFR 45 to < 60 mL/min/1.73 m ² . Discontinue therapy if eGFR falls below 45 mL/min/1.73 m ² .	Take before the first meal of the day.
JARDIANCE (empagliflozin)	Tablet: 10 mg, 25 mg	10 mg once daily in the morning. The dose may be increased to 25 mg in patients tolerating JARDIANCE.	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 .	Take with or without food.
Combination products				
INVOKAMET (canagliflozin/ metformin)	Tablets: 50/500 mg 50/1000 mg 150/500 mg 150/1000 mg	Recommended starting dose is 50 mg canagliflozin/500 mg metformin twice daily. Individual based on the patient's current regimen. Take twice daily with meals, with gradual dose escalation to reduce the GI side effects due to metformin.	Do not exceed a daily dose of metformin 2,000 mg and canagliflozin 300 mg. Assess renal function before initiating INVOKAMET. Limit canagliflozin to 50 mg twice daily in patients with eGFR of 45 to < 60 mL/min/1.73 m ² . Do not initiate INVOKAMET if eGFR is < 45 mL/min/1.73 m ² .	May need to discontinue at time of, or prior to, iodinated contrast imaging procedure in patients with an eGFR between 45 and 60 mL/min/1.73 m ² ; in patients with a history of liver disease, alcoholism or heart failure; in patients who will be administered intra-arterial iodinated contrast.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
INVOKAMET XR (canagliflozin/ metformin ER)	Tablets: 50/500 mg 50/1000 mg 150/500 mg 150/1000 mg	Take 2 tablets once daily with the morning meal. In patients currently not treated with either canagliflozin or metformin, initiate therapy with two INVOKAMET XR tablets, each containing canagliflozin 50 mg and metformin 500 mg. In patients already treated with canagliflozin and metformin, switch to two INVOKAMET XR tablets containing the same total daily dose of canagliflozin and the same, or nearest appropriate, total daily dose of metformin.	Do not exceed a daily dose of metformin 2,000 mg and canagliflozin 300 mg. Assess renal function before initiating INVOKAMET XR and periodically thereafter. Limit canagliflozin to 50 mg twice daily in patients with eGFR of 45 to < 60 mL/min/1.73 m ² . Do not initiate INVOKAMET XR if eGFR is < 45 mL/min/1.73 m ² .	May need to discontinue at time of, or prior to, iodinated contrast imaging procedure in patients with an eGFR between 45 and 60 mL/min/1.73 m ² ; in patients with a history of liver disease, alcoholism or heart failure; in patients who will be administered intra-arterial iodinated contrast. Swallow whole. Do not crush, cut, or chew.
XIGDUO XR (dapagliflozin/ metformin ER)	Tablets: 5/500 mg 5/1000 mg 10/500 mg 10/1000 mg	Individualize the starting dose based on the patient's current regimen. Take once daily in the morning with meals, with gradual dose escalation to reduce the GI side effects due to metformin.	Do not exceed a daily dose of metformin 2,000 mg and dapagliflozin 10 mg. In patients with volume depletion, correcting this condition prior to initiation of XIGDUO XR is recommended. Do not initiate if eGFR is < 60 mL/min/1.73 m ² .	Must be swallowed whole and never crushed, cut, or chewed. Take with food. May need to discontinue at time of, or prior to, iodinated contrast imaging procedure.
GLYXAMBI (empagliflozin/ linagliptin)	Tablets: 10/5 mg, 25/5 mg	Recommended starting dose is 10 mg empagliflozin/5 mg linagliptin once daily in the morning. May increase dose to 25 mg empagliflozin/5 mg linagliptin once daily.	Do not initiate or continue if eGFR < 45 mL/min/1.73 m ² .	Take with or without food.
SYNJARDY (empagliflozin/ metformin)	Tablets: 5/500 mg, 5/1000 mg, 12.5/500 mg, 12.5/1000 mg	Individualize the starting dose based on the patient's current regimen. Take twice daily with meals, with gradual dose escalation to reduce the GI	Do not exceed a daily dose of 25 mg empagliflozin/2000 mg metformin.	Take with meals. May need to discontinue at time of, or prior to, iodinated contrast imaging procedure in patients with an eGFR

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		side effects due to metformin.	Do not initiate if eGFR is < 45 mL/min/1.73 m ² .	between 45 and 60 mL/min/1.73 m ² ; in patients with a history of liver disease, alcoholism or heart failure; in patients who will be administered intra-arterial iodinated contrast.
SYNJARDY XR (empagliflozin/metformin ER)	Tablets: 5/1000 mg, 10/1000 mg, 12.5/1000 mg, 25/1000 mg	Individualize the starting dose based on the patient's current regimen. Take once daily with a meal in the morning, with gradual dose escalation to reduce the GI side effects due to metformin.	Do not exceed a daily dose of 25 mg empagliflozin/2000 mg metformin. Do not initiate if eGFR is < 45 mL/min/1.73 m ² .	Take with a meal. Swallow whole, do not split, crush, dissolve, or chew. May need to discontinue at time of, or prior to, iodinated contrast imaging procedure in patients with an eGFR between 45 and 60 mL/min/1.73 m ² ; in patients with a history of liver disease, alcoholism or heart failure; in patients who will be administered intra-arterial iodinated contrast.

eGFR=estimated glomerular filtration rate

SPECIAL POPULATIONS

Table 5. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
Single entity products					
FARXIGA (dapagliflozin)	No dosage change is recommended based on age.	Safety and effectiveness in pediatric patients < 18 years of age have not been established.	Treatment should not be initiated in patients with eGFR < 60 mL/min/1.73 m ² . Use of FARXIGA is not recommended in patients with eGFR falls persistently between 30 to < 60 mL/min/1.73 m ² .	No dose adjustment is recommended for patients with mild, moderate, or severe hepatic impairment. However, the benefits and risks for the use of dapagliflozin in patients with severe hepatic impairment should be	Pregnancy category C* (no data; potential benefits should justify the potential risk to fetus) Discontinue FARXIGA or discontinue nursing.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
				individually assessed since the safety and efficacy of dapagliflozin have not been specifically studied in this population.	
INVOKANA (canagliflozin)	<p>Patients aged ≥ 65 years had a higher incidence of adverse reactions related to reduced intravascular volume.</p> <p>Smaller reductions in HbA1c were seen patients aged ≥ 65 years.</p>	Safety and effectiveness in pediatric patients < 18 years of age have not been established.	<p>Treatment should not be initiated in patients with eGFR < 45 mL/min/1.73 m².</p> <p>Use of INVOKANA is not recommended in patients with eGFR is persistently < 45 mL/min/1.73 m².</p>	Not recommended with severe hepatic impairment.	<p>Females should be advised of the potential risk to fetus, especially during second and third trimesters.</p> <p>Not recommended when breastfeeding.</p>
JARDIANCE (empagliflozin)	<p>No Jardiance dosage change is recommended based on age.</p> <p>Decreased efficacy is expected in elderly patients with renal impairment.</p> <p>The risk of UTIs and volume-depletion adverse reactions increased in patients ≥ 75 years old.</p>	Safety and effectiveness in pediatric patients < 18 years of age have not been established.	<p>JARDIANCE should not be initiated in patients with an eGFR < 45 mL/min/1.73 m².</p> <p>Discontinue if eGFR is persistently < 45 mL/min/1.73 m².</p>	No dosing adjustment needed.	<p>Consider appropriate alternative therapies, especially during the second and third trimesters.</p> <p>Unknown if excreted in human milk.</p> <p>Not recommended when breastfeeding.</p>
Combination products					
INVOKAMET, INVOKAMET XR (canagliflozin/metformin)	There is a higher incidence of AEs related to reduced intravascular volume. Assess renal function more frequently.	Safety and effectiveness in pediatric patients < 18 years of age have not been established.	<p>Higher incidence of AEs related to reduced intravascular volume and renal function.</p> <p>Contraindicated in patients with moderate to severe renal impairment (eGFR < 45 mL/min/1.73 m²), end stage renal</p>	Not recommended in patients with hepatic impairment.	<p>Females should be advised of the potential risk to fetus, especially during second and third trimesters.</p> <p>There is no information regarding its presence in</p>

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
			disease, or patients on dialysis.		breast milk, effects on breastfed infant, or effects on milk production. Not recommended while breastfeeding.
GLYXAMBI (empagliflozin/linagliptin)	Empagliflozin is associated with osmotic diuresis, which could affect hydration in patients aged ≥ 75 years. No dose change is recommended.	Safety and effectiveness in pediatric patients < 18 years of age have not been established.	GLYXAMBI should not be initiated in patients with an eGFR < 45 mL/min/1.73 m ² . Discontinue if eGFR is < 45 mL/min/1.73 m ² .	No dosing adjustment needed.	Empagliflozin is not recommended during the second and third trimesters. Not recommended while breastfeeding.
SYNJARDY, SYNJARDY XR (empagliflozin/metformin)	There is a higher incidence of adverse reactions related to reduced renal function (e.g., UTIs and volume depletion) in patients aged ≥ 75 years. Renal function should be assessed more frequently in elderly patients. No dose change for empagliflozin is recommended.	Safety and effectiveness in pediatric patients < 18 years of age have not been established.	Contraindicated in patients with eGFR < 45 mL/min/1.73 m ² .	Not recommended with hepatic impairment.	Females should be advised of the potential risk to fetus, especially during second and third trimesters. Not recommended when breastfeeding. Advise premenopausal females of the potential for an unintended pregnancy.
XIGDUO XR (dapagliflozin/metformin)	No dosage change is recommended based on age.	Safety and effectiveness in pediatric patients < 18 years of age have not been established.	Contraindicated in patients with moderate to severe renal impairment (eGFR < 60 mL/min/1.73 m ²)	Not recommended with hepatic impairment.	Pregnancy category C* (no data; potential benefits should justify the potential risk to fetus)

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
			No dose adjustment is required in patients with mild renal impairment.		Discontinue nursing or XIGDUO XR.

eGFR=estimated glomerular filtration rate

*Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus. There are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

CONCLUSION

- Canagliflozin, dapagliflozin, and empagliflozin are inhibitors of sodium-glucose co-transporter 2 (SGLT2). SGLT2 is 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 type 2 diabetes mellitus (T2DM). SGLT2 inhibitors have demonstrated efficacy in lowering HbA1c levels by ~0.6% 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) is the first Food and Drug Administration (FDA)-approved SGLT2-inhibitor/dipeptidyl peptidase-4 inhibitor combination product. A 52-week, phase 3, double-blind, parallel-group, randomized-controlled trial in patients with T2DM demonstrated reductions in HbA1c with empagliflozin/linagliptin that were superior to those of empagliflozin or linagliptin alone as add-on to metformin (DeFronzo et al, 2015).
- In clinical trials, they 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, fasting plasma glucose, weight gain, post-prandial glucose, 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 estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m². Empagliflozin and canagliflozin are not recommended in patients with an eGFR < 45 mL/min/1.73 m². Volume depletion issues should be corrected prior to initiation of SGLT2 therapy.
- The SGLT2 inhibitors share a similar safety profile, including increased cholesterol levels, increased serum creatinine and a concomitant decrease in eGFR, volume depletion, and genital mycotic infections. A warning for bone fractures was added for canagliflozin-containing products recently. Warnings for diabetic ketoacidosis, urosepsis, and pyelonephritis were also added to the SGLT2 inhibitor labeling 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 (Garber et al, 2017; ADA 2017; Inzucchi et al, 2015).

- Evidence that glucose lowering reduces the rates of CV events and death has 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 myocardial infarction, 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, 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 (Zinman et al, 2015). Recently updated guidelines acknowledge the established CV benefit with empagliflozin (ADA, 2017; Garber et al, 2017).
- 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 (AEs) or risk for hypoglycemia. Positive CV outcomes have been demonstrated with empagliflozin, which suggest that it may play a significant role in T2DM patients at high risk for CV events. 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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