The Medical Letter®
on Drugs and Therapeutics

Comparison Chart: SODIUM-GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS

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SODIUM-GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS

DRUG	FORMULATIONS	USUAL ADULT DOSAGE	COST[1]
Canagliflozin – *Invokana* (Janssen)	100, 300 mg tabs	100 mg PO once daily, increase up to 300 mg once daily With UGT inducers* eGFR ≥60 mL/min/1.73 m^2: 200 mg once daily, may increase to 300 mg once daily if needed eGFR <60 mL/min/1.73 m^2: 200 mg once daily	$543.40
Dapagliflozin – *Farxiga* (AstraZeneca)	5, 10 mg tabs	Type 2 diabetes: 5 mg PO once daily, increase up to 10 mg once daily Heart failure and CKD: 10 mg PO once daily	532.80
Empagliflozin – *Jardiance* (Boehringer Ingelheim/Lilly)	10, 25 mg tabs	10 mg PO once daily, increase up to 25 mg once daily	548.50
Ertugliflozin – *Steglatro* (Merck)	5, 15 mg tabs	5 mg PO once daily, increase up to 15 mg once daily	309.60

*Uridine diphosphate-glucuronosyltransferase (UGT) inducers include rifampin, phenytoin, phenobarbital, and ritonavir.

RENAL DOSAGE ADJUSTMENTS

CANAGLIFLOZIN

eGFR 30 to <60 mL/min/1.73 m^2: 100 mg once/day
eGFR <30 mL/min/1.73 m^2:
- Initiation not recommended
- Patients with albuminuria (>300 mg/day) can continue 100 mg once/day

Dialysis: Contraindicated

DAPAGLIFLOZIN

eGFR 25 TO <45 mL/min/1.73 m^2:
- Not recommended to improve glycemic control in adults with type 2 diabetes
- For all other indications, 10 mg once/day

eGFR <25 mL/min/1.73 m^2:
- Initiation not recommended
- Can continue 10 mg once/day to reduce risk of eGFR decline, ESRD, CV death and hospitalization for heart failure

DIALYSIS: Contraindicated

EMPAGLIFLOZIN

eGFR <45 mL/min/1.73 m^2:
- Initiation not recommended
- Discontinue if eGFR is persistently in this range

eGFR <30 ml/min/1.73 m^2, ESRD, or Dialysis: Contraindicated

ERTUGLIFLOZIN

eGFR 30 to <60 mL/min/1.73 m^2:
- Initiation not recommended
- Discontinue if eGFR is persistently in this range

eGFR <30 ml/min/1.73 m^2, ESRD, or Dialysis: Contraindicated

CV = cardiovascular; CVD = cardiovascular disease; ESRD = end stage renal disease

ADMINISTRATION

- All are taken once daily
- All should be taken in the morning to avoid nocturia
- All (except canagliflozin) can be taken with or without food; canagliflozin should be taken before the first meal of the day
- Correct volume depletion before starting
- Consider temporarily stopping in cases of reduced oral intake (such as acute illness or fasting) or fluid loss (such as gastrointestinal illness or excessive heat exposure)

COMMENTS

- SGLT2 inhibitors decrease renal glucose reabsorption and increase urinary glucose excretion, reducing fasting and postprandial blood glucose levels
- Reduce A1C 0.5-1%
- Weight loss (0.1-4 kg)
- Reduce systolic blood pressure
- No hypoglycemia when used as monotherapy
- **Pregnancy:** no human data; affected renal development in animal studies

RENAL CONSIDERATIONS

- Efficacy decreases with worsening renal function
- Risk of renal adverse effects is increased in elderly patients and in those with renal impairment
- Acute kidney injury (requiring hospitalization and dialysis in some cases) has been reported with canagliflozin and dapagliflozin

SODIUM-GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS (continued)

CARDIOVASCULAR and RENAL INDICATIONS AND DATA

Drug	FDA Approval	Indication/Efficacy	Some Clinical Trials
With Type 2 Diabetes			
Canagliflozin	CV & Renal	▪ FDA-approved to reduce the risk of MACE in patients with established CVD ▪ FDA-approved to reduce the risk of end-stage kidney disease, doubling of serum creatinine, CV death, and hospitalization for heart failure in patients with diabetic nephropathy with albuminuria	CANVAS and CANVAS-R[2] CREDENCE[3]
Dapagliflozin	CV & Renal	▪ FDA-approved to reduce the risk of hospitalization for HF in patients with established CVD or multiple CV risk factors ▪ FDA-approved to reduce the risk of kidney function decline, renal failure, CV death and hospitalization for heart failure in patients with CKD who are at risk of disease progression	DECLARE-TIMI58[4]
Empagliflozin	CV only	▪ FDA-approved to reduce the risk of CV death in patients with established CVD ▪ Reduced the risk of incident or worsening nephropathy, doubling of serum creatinine, progression of kidney disease, progression to macroalbuminuria, initiation of renal-replacement therapy	EMPA-REG OUTCOME[5]
Ertugliflozin	No	▪ Noninferior to placebo for MACE	VERTIS-CV[6]
With or **Without** Type 2 Diabetes			
Canagliflozin	No	▪ None	None
Dapagliflozin	CV & Renal	▪ FDA-approved to reduce the risk of CV death and hospitalization for HF in patients with HFrEF ▪ FDA-approved to reduce the risk of kidney function decline, renal failure, CV death and hospitalization for heart failure in patients with CKD who are at risk of disease progression	DAPA-HF[7] DAPA-CKD[8]
Empagliflozin	No	▪ Lowered risk of CV death or hospitalization for HF ▪ Slowed the progression of renal disease	EMPEROR-Reduced[9]
Ertugliflozin	No	▪ None	None

CV = cardiovascular; CVD = cardiovascular disease; CKD = chronic kidney disease; HFrEF = heart failure with reduced ejection fraction; MACE = major adverse cardiovascular events (cardiovascular death, nonfatal MI, or nonfatal stroke)

SOME ADVERSE EFFECTS

- Genital mycotic infections
- Fournier's gangrene
- Volume depletion
- Acute kidney injury
- Hypotension
- Increased LDL-cholesterol
- Increased hemoglobin and/or hematocrit
- Ketoacidosis
- Increased risk of lower limb amputations with canagliflozin and ertugliflozin; SGLT2 inhibitors should generally not be used in patients at risk for foot amputation
- Possible increased fracture risk
- Dapagliflozin is contraindicated for use in patients with active bladder cancer

DRUG INTERACTIONS

Class:

- Hypoglycemia has occurred when used in combination with insulin and sulfonylureas

Canagliflozin:

- UGT inducers (e.g., rifampin, phenytoin, phenobarbital, ritonavir) decrease the AUC of canagliflozin and possibly its efficacy; canagliflozin dosage adjustments are recommended
- Canagliflozin could increase digoxin serum concentrations

Combinations with DPP-4 Inhibitors:

- Avoid concurrent use of strong CYP3A4 inhibitors with dapagliflozin/saxagliptin
- Avoid concurrent use of strong CYP3A4 or P-glycoprotein (P-gp) inducers with empagliflozin/linagliptin

SGLT2 INHIBITOR COMBINATION PRODUCTS

DRUG/FORMULATIONS	USUAL ADULT DOSAGE	DOSAGE ADJUSTMENTS	COST[1]
SGLT2 Inhibitor/Metformin Combinations			
Canagliflozin/metformin – *Invokamet* ▪ 50/500, 50/1000, 150/500, 150/1000 mg tabs **extended-release – *Invokamet XR*** ▪ 50/500, 50/1000, 150/500, 150/1000 mg ER tabs	50/500 mg-300/2000 mg PO twice daily with meals 100/1000 mg -300/2000 mg PO once daily in the morning with a meal	**eGFR 45 to <60 mL/min/1.73 m²:** Canagliflozin 100 mg daily **eGFR 30 to <45 mL/min/1.73 m²:** Initiation not recommended Assess benefit/risk of continuation Limit dose of canagliflozin to 100 mg daily **eGFR <30 mL/min/1.73 m², ESRD, or Dialysis:** Contraindicated **UGT Inducers:** See canagliflozin above	$543.40 543.40
Dapagliflozin/metformin – *Xigduo XR* ▪ 2.5/1000, 5/500, 5/1000, 10/500, 10/1000 mg ER tabs	5/500-10/2000 mg PO once daily in the morning with the first meal of the day	**eGFR 30 to <45 mL/min/1.73 m²:** Not recommended **eGFR <30 mL/min/1.73 m², ESRD, or Dialysis:** Contraindicated	532.80
Empagliflozin/metformin – *Synjardy* ▪ 5/500, 5/1000, 12.5/500, 12.5/1000 mg tabs **extended-release – *Synjardy XR*** ▪ 5/1000, 10/1000, 12.5/1000, 25/1000 mg ER tabs	5/500-12.5/1000 mg PO bid with meals 5/1000-25/2000 mg PO once daily in the morning with a meal	**eGFR <45 mL/min/1.73 m², ESRD, or Dialysis:** Contraindicated	548.50 548.50
Ertuglflozin/metformin – *Segluromet* ▪ 2.5/500, 2.5/1000, 7.5/500, 7.5/1000 mg tabs	2.5/500-7.5/1000 mg PO bid with meals	**eGFR 30 to <60 mL/min/1.73 m²:** Initiation not recommended Discontinue if eGFR is persistently in this range **eGFR <30 mL/min/1.73 m², ESRD, or Dialysis:** Contraindicated	309.60
SGLT2 Inhibitor/DPP-4 Inhibitor Combinations			
Dapagliflozin/saxagliptin – *Qtern* ▪ 5/5, 10/5 mg tabs	5/5-10/5 mg PO once daily in the morning, with or without food	**eGFR <45 mL/min/1.73 m², ESRD, or Dialysis:** Contraindicated	532.80
Empagliflozin/linagliptin – *Glyxambi* ▪ 10/5, 25/5 mg tabs	10/5-25/5 mg PO once daily in the morning, with or without food	**eGFR <45 mL/min/1.73 m², ESRD, or Dialysis:** Initiation not recommended Discontinue if eGFR is persistently in this range **eGFR <30 mL/min/1.73 m², ESRD, or Dialysis:** Contraindicated	548.50
Ertugliflozin/sitagliptin – *Steglujan* ▪ 5/100, 15/100 mg tabs	5/100-15/100 mg PO once daily in the morning, with or without food	**eGFR 30 to <60 mL/min/1.73 m²:** Initiation not recommended Discontinue if eGFR is persistently in this range **eGFR <30 mL/min/1.73 m², ESRD, or dialysis:** Contraindicated	549.90

METFORMIN ADVERSE EFFECTS

- GI effects (metallic taste, nausea, diarrhea, abdominal pain); take with food to reduce the severity of GI adverse effects
- Vitamin B12 deficiency
- Rarely lactic acidosis

▶Metformin should be not be administered for 48 hours after an iodinated contrast imaging procedure in patients with an eGFR <60 mL/min/1.73 m² or a history of liver disease, alcoholism, or heart failure, or in those receiving intra-arterial contrast, and eGFR should be re-evaluated before treatment is

DPP-4 INHIBITOR ADVERSE EFFECTS

- Possible risk of acute pancreatitis
- Fatal hepatic failure
- Possible worsening heart failure
- Possible severe and disabling joint pain

References:

1. Approximate WAC for 30 days' treatment with the lowest usual dosage. WAC = wholesale acquisition cost, or manufacturer's published price to wholesalers; WAC represents published catalogue or list prices and may not represent actual transactional prices. Source: Analysource® Monthly. May 5, 2021. Reprinted with permission by First Databank, Inc. All rights reserved. ©2021. www.fdbhealth.com/policies/drug-pricing-policy.
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