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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 – <i>Invokana</i> (Janssen)	100, 300 mg tabs	100 mg PO once daily, increase up to 300 mg once daily <u>With UGT inducers*</u> 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 – <i>Farxiga</i> (AstraZeneca)	5, 10 mg tabs	<u>Type 2 diabetes</u> : 5 mg PO once daily, increase up to 10 mg once daily <u>Heart failure and CKD</u> : 10 mg PO once daily	532.80
Empagliflozin – <i>Jardiance</i> (Boehringer Ingelheim/Lilly)	10, 25 mg tabs	10 mg PO once daily, increase up to 25 mg once daily	548.50
Ertugliflozin – <i>Steglatro</i> (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.

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 DOSAGE ADJUSTMENTS

CANAGLIFLOZIN

eGFR 30 to <60 mL/min/1.73 m²: 100 mg once/day

eGFR <30 mL/min/1.73 m²:

- 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 m²:

- 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 m²:

- 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 m²:

- Initiation not recommended
- Discontinue if eGFR is persistently in this range

eGFR <30 mL/min/1.73 m², ESRD, or Dialysis: Contraindicated

ERTUGLIFLOZIN

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

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

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-R² CREDENCE³
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-TIMI58⁴
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 OUTCOME⁵
Ertugliflozin	No	Noninferior to placebo for MACE	VERTIS-CV⁶
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-HF⁷ DAPA-CKD⁸
Empagliflozin	No	- Lowered risk of CV death or hospitalization for HF - Slowed the progression of renal disease	EMPEROR-Reduced⁹
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

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

SGLT2 INHIBITOR COMBINATION PRODUCTS			
DRUG/FORMULATIONS	USUAL ADULT DOSAGE	DOSAGE ADJUSTMENTS	COST ¹
SGLT2 Inhibitor/Metformin Combinations			
Canagliflozin/metformin – <i>Invokamet</i> ■ 50/500, 50/1000, 150/500, 150/1000 mg tabs	50/500 mg-300/2000 mg PO twice daily with meals	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
extended-release – <i>Invokamet XR</i> ■ 50/500, 50/1000, 150/500, 150/1000 mg ER tabs	100/1000 mg -300/2000 mg PO once daily in the morning with a meal		543.40
Dapagliflozin/metformin – <i>Xigduo XR</i> ■ 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 – <i>Synjardy</i> ■ 5/500, 5/1000, 12.5/500, 12.5/1000 mg tabs	5/500-12.5/1000 mg PO bid with meals	eGFR <45 mL/min/1.73 m², ESRD, or Dialysis: Contraindicated	548.50
extended-release – <i>Synjardy XR</i> ■ 5/1000, 10/1000, 12.5/1000, 25/1000 mg ER tabs	5/1000-25/2000 mg PO once daily in the morning with a meal		548.50
Ertugliflozin/metformin – <i>Segluromet</i> ■ 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 – <i>Qtern</i> ■ 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 – <i>Glyxambi</i> ■ 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 – <i>Steglujan</i> ■ 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 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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