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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.

| 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 : <ul style="list-style-type: none"> 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 : <ul style="list-style-type: none"> 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 : <ul style="list-style-type: none"> 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 : <ul style="list-style-type: none"> 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 m ² : <ul style="list-style-type: none"> 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 |

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 | <ul style="list-style-type: none"> 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 CREDESCENCE ³ |
| Dapagliflozin | CV & Renal | <ul style="list-style-type: none"> 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 | <ul style="list-style-type: none"> 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 | <ul style="list-style-type: none"> Noninferior to placebo for MACE | VERTIS-CV ⁶ |
| With or Without Type 2 Diabetes | | | |
| Canagliflozin | No | <ul style="list-style-type: none"> None | None |
| Dapagliflozin | CV & Renal | <ul style="list-style-type: none"> 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 | <ul style="list-style-type: none"> Lowered risk of CV death or hospitalization for HF Slowed the progression of renal disease | EMPEROR-Reduced ⁹ |
| Ertugliflozin | No | <ul style="list-style-type: none"> 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 extended-release – <i>Invokamet XR</i> ■ 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 – <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 extended-release – <i>Synjardy XR</i> ■ 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 |
| 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.
2. B Neal et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017; 377:644.
3. V Perkovic et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019; 380: 2295.
4. SD Wiviott et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019; 380:347.
5. B Zinman et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015; 373:2117.
6. CP Cannon et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. *N Engl J Med* 2020; 383:1425.
7. JJV Murray et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019; 381:1995.
8. HJL Heerspink et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020; 383:1436.
9. M Packer et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020; 383:1413.