

Empagliflozin (JARDIANCE) Criteria for Use

VA Pharmacy Benefits Management Services, Medical Advisory Panel and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.**

Exclusion Criteria

- History of a serious hypersensitivity reaction to an SGLT2 inhibitor
- Estimated GFR (eGFR) < 45ml/min/1.73m²
- On dialysis
- Pregnant or nursing
- Pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, recurrent pancreatitis, pancreatic surgery)
- History of frequent UTIs, those with indwelling catheters, need for self-catheterization, or known history of increased post void residual
- A1C <7% or >10%

Inclusion Criteria for those WITH Cardiovascular Disease

- Type 2 diabetes
- A1C not at goal AND receiving metformin or another hypoglycemic agent if unable to use metformin^{1,2}

AND at least ONE of the following (see Appendix for definition of high risk cardiovascular events used in the EMPA-REG clinical trial):

- History of established clinically relevant coronary artery disease
- History of stroke
- History of symptomatic occlusive peripheral artery disease

¹ Refer to the VA/DoD Diabetes Guidelines <http://www.healthquality.va.gov/index.asp> for recommendations on individualizing A1C targets

² The cardiovascular benefits of empagliflozin have been demonstrated in the EMPA-REG clinical trial. However, achieving and maintaining glycemic control remains a major goal in the management of patients with type 2 diabetes. Average expected change in hemoglobin A1c (A1C) is < 1% with the SGLT2 inhibitors. If the desired reduction in A1C is beyond what is achievable by empagliflozin, additional interventions (i.e., dietary, exercise, antihyperglycemic agents) are generally required.

Inclusion Criteria for those WITHOUT Cardiovascular Disease

- Type 2 diabetes
- Expected change in A1C <1% in order to achieve patient specific goal³

AND the following:

Add-on therapy as part of an oral 2 drug regimen

- Inadequate glycemic control on metformin or other hypoglycemic agent if unable to use metformin
- Unable to tolerate or has contraindications to addition of a sulfonylurea, DPP-4 inhibitor, and pioglitazone

OR

Add-on therapy as part of an oral 3-drug regimen (all 3 must be selected)

- Inadequate glycemic control on combination therapy with any 2 of the following drugs: metformin, sulfonylurea, pioglitazone, and DPP-4 inhibitor
- Unable to tolerate or has contraindications to addition of a 3rd agent from the above mentioned group
- Patient is not a good candidate for addition of insulin OR declines insulin despite counseling and, when feasible, instruction and demonstration of insulin technique by a diabetes educator or other appropriate clinician⁴

Use with Insulin

Discontinuation of empagliflozin when insulin is initiated or addition of empagliflozin to existing insulin therapy should be made on a case-by-case basis

³ Refer to the VA/DoD Diabetes Guidelines <http://www.healthquality.va.gov/index.asp> for recommendations on individualizing A1C targets

⁴ Examples include circumstances where the risk of severe hypoglycemia and or potential consequences are significant and or catastrophic (e.g., frail elderly, liver failure, workers with frequent rotating shifts, occupations such as truck or bus drivers, or heavy machinery operator, etc.) or unable to master injection technique

Dosage

Refer to product labeling for dosing information

Issues for Consideration

Hypotension: SGLT2 inhibitors cause intravascular volume contraction. Symptomatic hypotension may occur after initiation of the SGLT2 inhibitor particularly in patients with eGFR <60mL/min/1.73m², elderly patients, those taking diuretics, or have low systolic blood pressure. Volume status should be assessed and corrected before initiating an SGLT2 inhibitor in patients with these characteristics. Monitor for signs and symptoms after initiating therapy.

Ketoacidosis: There have been postmarketing reports of ketoacidosis, often with blood glucose levels <250mg/dL. Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If suspected, discontinue the SGLT2 inhibitor, evaluate and treat promptly. Before initiating a SGLT2 inhibitor, consider risk factors for ketoacidosis (e.g., pancreatic insulin deficiency, alcohol abuse, caloric restriction). Patients on a SGLT2 inhibitor may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis such as prolonged fasting due to acute illness or surgery.

Impairment in renal function: SGLT2 inhibitors can increase serum creatinine and decrease eGFR. Elderly patients, those with impaired renal function or hypovolemia may be more susceptible to these changes. Periodic monitoring of renal function is recommended. More frequent monitoring is recommended in patients with eGFR <60mL/min/1.73m².

Urosepsis and Pyelonephritis: SGLT2 inhibitors increase the risk of urinary tract infections. There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis in patients receiving SGLT2 inhibitors. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.

Genital mycotic infections: SGLT2 inhibitors increase the risk of genital mycotic infections. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections. Uncircumcised males were at a higher risk for developing genital mycotic infections.

Hypersensitivity reactions: Hypersensitivity reactions (e.g., generalized urticaria), some serious, have been reported. If hypersensitivity reactions occur, discontinue use and treat per standard of care. If the reaction was serious, the SGLT2 inhibitor should not be restarted (see contraindications).

Increase in low-density lipoprotein (LDL-C): Dose-related increases in LDL-C occur. Monitor LDL-C and treat per standard of care.

Increase in hematocrit: SGLT2 inhibitors may cause an increase in hematocrit resulting from intravascular volume contraction. The available evidence shows no increase in thromboembolic events.

Pregnancy Category C: In rat studies, SGLT2 inhibitors may affect renal development and maturation. The timing of these effects corresponds to 2nd and 3rd trimester of human development; therefore consider alternate therapy during pregnancy especially during the 2nd and 3rd trimester.

Lactation: The SGLT2 inhibitors are secreted in milk of lactating rats. It is not known if they are excreted in human milk. Data in juvenile rats showed risk to the developing kidney during maturation. In humans, kidney maturation occurs *in utero* and in the first 2 years of life. Because of the potential for serious adverse reactions to the nursing infant, a decision should be made to discontinue the SGLT2 inhibitor or nursing taking into account the importance of the drug to the mother.

Empagliflozin dose-response effect: There appears to be little difference in efficacy between the 10mg and 25mg dose. The difference in mean A1C reduction between the two doses is generally <0.2%. In the EMPA-REG trial the number needed to treat during a 3-year period to prevent 1 death was 41 (10mg) and 38 (25mg).

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Appendix: Definition of High Risk Cardiovascular Events used in the EMPA-REG Trial

- History of MI >2 months prior to informed consent
- Evidence of multi-vessel CAD i.e. in ≥ 2 major coronary arteries or the left main coronary artery,
- documented by any of the following:
 - Presence of significant stenosis: $\geq 50\%$ luminal narrowing during angiography (coronary or multi-slice computed tomography)
 - Previous revascularization (percutaneous transluminal coronary angioplasty \pm stent or coronary artery bypass graft >2 months prior to consent
 - The combination of revascularization in one major coronary artery and significant stenosis ($\geq 50\%$ luminal narrowing) in another major coronary artery
- Evidence of single-vessel coronary artery disease, $\geq 50\%$ luminal narrowing during angiography (coronary or multi-slice computed tomography) not subsequently successfully revascularized, with at least 1 of the following:
 - A positive non-invasive stress test for ischemia
 - Hospital discharge for unstable angina ≤ 12 months prior to consent
- Unstable angina >2 months prior to consent with evidence of single- or multi-vessel CAD
- History of stroke (ischemic or hemorrhagic) >2 months prior to consent
- Occlusive peripheral artery disease documented by any of the following:
 - Limb angioplasty, stenting, or bypass surgery
 - Limb or foot amputation due to circulatory insufficiency
 - Evidence of significant peripheral artery stenosis ($>50\%$ on angiography, or $>50\%$ or hemodynamically significant via non-invasive methods) in 1 limb
 - Ankle brachial index < 0.9 in ≥ 1 ankle