Empagliflozin 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) < 45 ml/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

#### Patients WITH Cardiovascular Disease (All must be selected)
- Type 2 diabetes
- A1C not at goal AND receiving metformin or another agent if unable to use metformin
- Established cardiovascular disease (Appendix 1 may be used as a guide for clinical judgement)

#### Patients WITHOUT Cardiovascular Disease
- Type 2 diabetes
- Inadequate glycemic control on two oral medications, one of which should be metformin, or another agent if unable to use metformin
  - OR
- Inadequate glycemic control on optimally titrated on basal insulin therapy + metformin or another agent if unable to use metformin


2Insulin may be considered at any time prior to using empagliflozin; however, insulin is preferred if patient is symptomatic or the desired A1C reduction is beyond what is achievable by empagliflozin. In clinical trials the mean reduction in A1C when empagliflozin is used alone or added to oral hypoglycemic agents ranges from 0.7%-0.8%.

3Empagliflozin is approved for reducing the risk of cardiovascular death in patients with type 2 diabetes and established cardiovascular disease as 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. If the desired reduction in A1C is beyond what is achievable by empagliflozin, additional interventions (i.e., dietary, exercise, antihyperglycemic agents) are generally required.

4Basal insulin should be titrated as feasible to an acceptable fasting blood glucose level unless unable to (e.g., hypoglycemia, patient unwilling or unable to intensify insulin dose)

5Consider addition of mealtime insulin; however, mealtime insulin should be used if patient is symptomatic or the desired A1C reduction is beyond what is achievable by empagliflozin. In clinical trials the mean reduction in A1C when empagliflozin is added to insulin ± metformin (and/or sulfonylureas) ranged from 0.6% to 1.0%.

### 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., pancreatitis, 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.

**Fournier’s Gangrene:** Between March 2013 up to May 2018 12 cases of Fournier’s gangrene occurred in patients taking an SGLT2 inhibitor. Seven cases occurred in men and five in women, all which required hospitalization and surgery (one patient died). The average time to onset was 9.2 months (range 7 days to 25 months).

FDA indicates that this adverse event is very rare, with an estimated 1.7 million patients prescribed an SGLT2 inhibitor in 2017. Providers should instruct patients to promptly seek medical attention if they experience any symptoms of tenderness, erythema, or swelling in the genital or perineal area, fever, or malaise.

**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).

**Amputation:** Data from the CANVAS trials found that the use of canagliflozin was associated with approximately two-fold increased risk of lower limb amputations. Amputations most commonly occurred with the toe and middle of the foot but also involved the leg, below and above the knee. Some patients had more than one amputation and both limbs may have been affected. Events observed in the trials that preceded the need for amputation included lower limb infections, gangrene, diabetic foot ulcers, and ischemia.

The labeling for canagliflozin includes a **Boxed Warning** recommending the following: Before initiating, consider factors that may increase the risk of amputation such as a history of prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers. Monitor patients receiving canagliflozin for infections or ulcers of the lower limbs, and discontinue if these occur. Instruct patients to notify their health care professionals right away if they notice any new pain or tenderness, sores or ulcers, or infections in their legs or feet.

It is not known whether the increased risk extends to other SGLT2 inhibitors such as the VANF agent empagliflozin. While an increase in lower extremity amputations has not been reported for empagliflozin, additional study is needed to assess if amputations are a class effect or limited to canagliflozin.

**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).

Follow-up
Reassess improvement in glycemic goals (e.g., A1C, postprandial glucose) and other nonglycemic improvement such as weight loss

Appendix 1: Eligibility Criteria for Established Cardiovascular Disease 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: ≥50% luminal narrowing during angiography (coronary or multi-slice computed tomography)
  - Previous revascularization (percutaneous transluminal coronary angioplasty ± stent or coronary artery bypass graft >2 months prior to consent
  - The combination of revascularization in one major coronary artery and significant stenosis (≥50% luminal narrowing) in another major coronary artery
- Evidence of single-vessel coronary artery disease, ≥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

**Please see Issues for Consideration: Amputation

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