Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Update: SGLT-2 Inhibitors

Date of Review: August 2021

Date of Last Review: August 2020
Dates of Literature Search: 04/01/2020 - 05/17/2020

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
There have been updated indications for drugs in the sodium-glucose cotransporter 2 (SGLT2) inhibitor class as well as additional literature published since the last review in August of 2020. The purpose of this update is to analyze the new evidence and update policy if needed.

Research Questions:
- In patients with type 2 diabetes (T2D), is there any new comparative efficacy or harms evidence for SGLT2 inhibitors (e.g., hemoglobin A1c [A1C], microvascular outcomes, macrovascular outcomes and mortality)?
- Are there subpopulations of patients with T2D for which SGLT2 inhibitors may be more effective or associated with less harm?

Conclusions:
- There were 2 new systematic reviews and meta-analyses, 5 randomized controlled trials, 2 new safety updates and 2 new indications identified in this review.
- There is moderate quality evidence that SGLT2 inhibitors reduce the risk of all-cause mortality, cardiovascular (CV) mortality and hospitalizations for heart failure (HF) in patients, irrespective of T2D diagnosis or HF diagnosis, based on evidence from 2 systematic reviews and meta-analyses.[1,2]
- The evidence for the use of SGLT2 inhibitors for reduction in risk of myocardial infarction (MI) is less robust, with analyses suggesting a modest benefit (hazard ratio [HR] 0.91; 95% confidence interval [CI], 0.84 to 0.99; p=0.03).[2]
- Subgroup analyses found that SGLT2 inhibitors were more effective than placebo in reducing all-cause mortality and CV mortality in patients with HF, independent of diabetes diagnosis, ejection fraction or renal function.[1]
- There was moderate quality of evidence that SGLT2 inhibitors are associated with a higher risks of diabetic ketoacidosis and genital infections, compared to placebo.[2]
- One randomized controlled trial (RCT) demonstrated modest quality evidence that empagliflozin was more effective than placebo at reducing CV death or hospitalization for HF in patients with and without diabetes (absolute risk reduction [ARR] 5.3%/number needed to treat [NNT] 19 over 16 months).[3]
- Ertugliflozin demonstrated no CV risk or benefit compared to placebo based on moderate evidence from one RCT.[4]

Author: Kathy Sentena, PharmD

- Dapagliflozin was more effective than placebo at reducing the risk of progression of chronic kidney disease (CKD) in patients, with and without diabetes, followed for a mean of 2.4 years based on moderate evidence (ARR 5.3%/NNT 19).[5] Findings led to an additional indication as described below.
- Moderate evidence demonstrated dapagliflozin was more effective than placebo (HR 0.74;95% CI, 0.65 to 0.85; ARR 4.9%/ NNT 21 over a median follow up of 18.2 months) at reducing the risk of worsening HF or death from CV causes in patients with and without diabetes with HF and reduced ejection fraction based on one RCT.[6] Findings led to an additional indication as described below.
- Canagliflozin reduced the risk of kidney failure and CV events more than placebo, 43.2 events per 1000 patient-years compared to 61.2 events per 1000 patient years, respectively, in patients with T2D and kidney disease, based on moderate evidence.[7]
- There was a new safety update for the SGLT2 class that warns of an increased risk of ketoacidosis after surgery. The recommendation is that SGLT2 inhibitors should be stopped at least 3-4 days (drug dependent) prior to surgery.[8]
- Prescribing information for canagliflozin was updated in August of 2020 to remove the boxed warning for increased risk of lower limb amputation.[9]

Recommendations:
- No changes to the preferred drug list (PDL) are warranted based on the evidence identified since the last review.
- After evaluation of comparative costs in executive session, no PDL changes were recommended.

Summary of Prior Reviews and Current Policy:
- In August of 2020 a review was done to summarize findings from the Oregon Health and Science University (OHSU) Drug Effectiveness Review Project on Newer Diabetes Drugs and Cardiovascular Disease Outcomes. Findings from the report included literature up to October 2, 2019, which captured many trials related to the cardiovascular effects of SGLT2 inhibitors. Important findings were:
    - Canagliflozin, dapagliflozin, and empagliflozin reduced risks of hospitalization due to HF (NNT 42-80).
    - Empagliflozin reduced all-cause mortality compared to placebo, 5.7% vs. 8.3% (HR 0.68; 95% CI, 0.57 to 0.82; P <0.001; ARR 2.6%/ NNT 38 over a median follow up of 3.1 years.
    - Canagliflozin reduced hemorrhagic stroke in patients with preexisting cerebrovascular disease (HR 0.43; 95% CI, 0.20 to 0.89; P=0.02).
- After executive session all the SGLT2 inhibitors as single agents (excluding combinations) were designated preferred with the exception of ertugliflozin.

Background:
SGLT-2 inhibitors modestly lower A1C, approximately -0.5% in placebo-controlled comparisons, in patients with T2D by increasing urinary glucose excretion.[10] They are used as a second-line pharmacotherapy option after metformin and lifestyle modifications. SGLT-2 inhibitors are unlikely to cause hypoglycemia and have modest benefits on blood pressure reduction and weight loss. There is also evidence of benefit on CV and renal outcomes in patients with and without diabetes (**Table 1**). While not all SGLT-2 inhibitors have been studied or demonstrated additional benefits beyond glucose lowering, the benefits are thought to be a class effect.

Table 1. Sodium-glucose Co-transporter 2 Inhibitors

Generic Name	Brand Name	Evidence for Use	Indications
Canagliflozin[9]	INVOKANA	- CKD in patients with T2DM - CV risk in patients with T2DM	- Improve glycemic control in adults with T2D - Reduce the risk of major CV events in adults with T2D and established CV disease

			- Reduce the risk of end-stage kidney disease in patients with T2D and diabetic nephropathy with albuminuria > 300 mg/day
Dapagliflozin[11]	FARXIGA	- CKD in patients with and without T2DM - CV risk in patients with T2DM - Reduced risk of HF in HFrEF patients with and without T2DM	- Improve glycemic control in adults with T2D - Reduce the risk of hospitalization for HF in patients with T2D and established CV disease or multiple CV risk factors - Reduce the risk of CV death and hospitalization for HF in adults with HF and HFrEF - Reduce the risk of eGFR decline and end-stage kidney disease CV death and hospitalization for HF in adults with CKD at risk of progression
Empagliflozin[12]	JARDIANCE	- CKD in patients without T2DM - CV risk in patients with T2DM - Reduced risk of heart failure in patients with and without T2DM	- Improve glycemic control in adults with T2D - Reduce the risk of CV death in adults with T2D and established CV disease
Ertugliflozin[13]	STEGLATRO	- Neutral CV effect	- Improve glycemic control in adults in adults with T2D
Abbreviations: CKD – chronic kidney disease; CV – cardiovascular; HFrEF – heart failure with reduced injection fraction; T2D – type 2 diabetes			

Common treatment emergent adverse events with SGLT-2 inhibitors include urinary tract infections, yeast infections, and foot ulcerations. It is not recommended to use SGLT-2 inhibitors in those at risk of diabetic ketoacidosis or those at risk of foot amputation.[10] SGLT-2 inhibitors should not be used in patients with an estimated glomerular filtration rate (eGFR) of < 60 mL/min/1.73 m^2 for ertugliflozin, < 45 mL/min/1.73 m^2 for dapagliflozin and empagliflozin or < 30 mL/min/1.73 m^2 for canagliflozin. Hypovolemia and acute kidney injury have been reported in patients taking diuretics and in the elderly. SGLT-2 inhibitors should be discontinued before any scheduled surgery to avoid risk of ketoacidosis (see **Table 7** below).

Outcomes used to validate efficacy of SGLT-2 inhibitors include A1C, mortality, hospitalizations, reduction in CV risk, reduction in CKD, hypoglycemia, genital infections, amputations, volume depletion and ketoacidosis.

The SGLT2 inhibitor class represents a modest expenditure to the Oregon Health Authority (OHA). There were 46 claims last quarter with 100% PDL compliance.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

Cardoso, et al – SGLT2 Inhibitors Decrease Cardiovascular Death and Heart Failure Hospitalizations in Patients with Heart Failure: A Systematic Review and Meta-analysis

A 2021 systematic review and meta-analysis analyzed the effect of SGLT2 inhibitors in patients with HF, without regard to diabetes diagnosis, on mortality and hospitalization endpoints. One author, of seven, had declared conflicts of interest.[1] Literature was searched through January 21, 2021, identifying 15 RCTs (n=20,241). The following medications were included in the review: canagliflozin (2 trials), dapagliflozin (4 trials), empagliflozin (6 trials), ertugliflozin (1 trial) and sotagliflozin (2 trials). All trials were placebo-controlled. Mean follow-up was 3 to 50.4 months.[1] Four studies included patients with heart failure with preserved ejection fraction (HFpEF) (left ventricular ejection fraction [LVEF] cutoffs varied from ≥45% to ≥50%). Risk of bias assessment demonstrated low risk of bias for all domains for all studies. Funnel plot analysis found no indication of publication bias.

Results of the systematic review and meta-analysis are presented in **Table 2.**[1] SGLT2 inhibitors were more effective than placebo for all outcomes studied. Subgroup analysis found a benefit of SGLT2 inhibitors compared to placebo in patients with diabetes (HR 0.74; 95% CI 0.68 to 0.80; p<0.0001) and in those without diabetes (HR 0.74; 95% CI, 0.63 to 0.86; p=0.0002).[1] There was also consistent benefit of SGLT2 inhibitors compared to placebo for estimated glomerular filtration rate (eGFR) <60 and eGFR ≥60, New York Heart Association (NYHA) class II or NYHA class III-IV, HFpEF and in those with reduced ejection fraction (EF). There were no significant differences between SGLT 2 inhibitors and placebo for the outcomes of amputations or bone fractures. More patients randomized to SGLT2 inhibitors experienced weight loss compared to those taking placebo (mean difference -1.11 kg; 95% CI, -1.41 to -0.82; p<0.0001).[1]

Table 2. Meta-analysis Finding of SGLT2 Inhibitors and Cardiovascular Death and Heart Failure[1]

Outcome	Results*	Interpretation
All-cause mortality	HR 0.86 (95% CI, 0.79 to 0.94); p = 0.0007	SGLT2 inhibitors were more effective than placebo in reducing all-cause mortality
Cardiovascular mortality	HR 0.86 (95% CI, 0.78 to 0.96); p = 0.006	SGLT2 inhibitors were more effective than placebo in reducing CV mortality
Hospitalizations for HF	HR 0.69 (95% CI, 0.62 to 0.76); p < 0.0001	SGLT2 inhibitors were more effective than placebo in reducing hospitalizations for HF
Urgent visits for HF	HR 0.39 (95% CI, 0.22 to 0.69); p = 0.001	SGLT2 inhibitors were more effective than placebo in reducing urgent visits for HR
Composite endpoint of CV mortality or hospitalizations for HF	HR 0.75 (95% CI, 0.70 to 0.80); p < 0.0001	SGLT2 inhibitors were more effective than placebo in reducing CV mortality or hospitalization for HF

Abbreviations: CI – confidence interval; CV – cardiovascular; HF – heart failure; HR – hazard ratio

Key: * Absolute risk reductions not available

Limitations to this review include no discussion of publication bias or risk of bias assessments. Additionally, all trials were graded as low risk of bias for all domains, which suggests potential bias since critical evaluation of the literature seldom results in these findings.

Salah, et al – Effect of Sodium-glucose Cotransporter 2 Inhibitors on Cardiovascular and Kidney Outcomes

A 2020 systematic review and meta-analysis analyzed the effect of SGLT2 inhibitors on CV and kidney outcomes in patients irrespective of diabetes diagnosis, patients with HF, and patients with chronic kidney disease.[2] The review methodology was clearly described and evidence was graded and assessed for risk of bias. Six of 11 authors had conflicts of interest. Literature was searched through September 24, 2020 which yielded 8 (n=59,747) randomized, placebo-controlled

trials.[2] Three trials evaluated dapagliflozin, 3 evaluated canagliflozin, 2 trials evaluated empagliflozin and one trial evaluated ertugliflozin. Two trials included patients with heart failure with reduced ejection fraction (HFrEF), irrespective of diabetes status, and 5 trials required a T2D diagnosis for inclusion.

Results for the systematic review and meta-analysis are presented in **Table 3**.[2] The overall quality of evidence was rated as moderate to high for all outcomes. The use of SGLT2 inhibitors in patients, with and without diabetes, was found to reduce the risk of adverse CV and kidney outcomes for all analyses except for stroke, in which there was no difference. In subgroup analyses of patients with T2D, with and without HF, the results were similar to those presented in **Table 3**. In patients with T2D and heart failure, the findings were also similar to those presented in **Table 3**, with the exception that there was no difference in the risk of stroke or MI between the two groups. There was no benefit in all-cause mortality, CV mortality, MI, or stroke for SGLT2 inhibitors for patients with T2D and no HF, although there was a decreased risk of hospitalizations for HF and reduction in the composite kidney outcome (end-stage kidney disease, a doubling of serum creatinine level, or kidney related mortality).[2] Patients with HF, irrespective of T2D diagnosis, had similar results to those presented in **Table 3**, with the exception of no risk reduction with SGLT2 inhibitors for the outcomes of MI and stroke. Patients with CKD (eGFR 60 mL/min/1.73 m^2 or less) found benefit with the use of SGLT2 inhibitors for reducing the risk of hospitalizations for heart failure, MI and reducing the reduction in the composite kidney outcome. Those patients that had no history of kidney disease (eGFR 60 mL/min/1.73 m^2 or greater) were found to have benefit from SGLT2 inhibitor therapy for the outcomes of reduction in the risk of hospitalization for HF and risk of experiencing the composite kidney outcome.

The risk of hypoglycemia or amputation with SGLT2 inhibitors was not statistically different from placebo. SGLT2 inhibitors demonstrated a risk of diabetic ketoacidosis in 0.23% of patients compared to 0.8% with placebo.[2] The risk of genital infections was also higher with SGLT2 inhibitors (OR 3.95; 95% CI, 3.01 to 5.18; moderate quality of evidence).[2]

Table 3. Meta-analysis Results for the Use of SGLT2 Inhibitors on Cardiovascular and Kidney Outcomes[2]

Outcome	Results	Quality of Evidence	Interpretation
All-cause mortality	HR 0.85 (95% CI, 0.78 to 0.91); p < 0.0001	Moderate	SGLT2 inhibitors were more effective than placebo at reducing all-cause mortality
Cardiovascular mortality	HR 0.84 (95% CI, 0.76 to 0.93); p = 0.007	Moderate	SGLT2 inhibitors were more effective than placebo at reducing CV mortality
Hospitalizations for HF	HR 0.69 (95% CI, 0.64 to 0.74); p < 0.00001	High	SGLT2 inhibitors were more effective than placebo at reducing hospitalizations for HF
Myocardial Infarction	HR 0.91 (95% CI, 0.84 to 0.99); p=0.03	High	SGLT2 inhibitors were slightly more effective than placebo at reducing risk of MI
Composite Kidney Outcome (end-stage kidney disease, a doubling of serum creatinine level, or kidney related mortality)	HR 0.62 (95% CI, 0.56 to 0.70); p=0.72	Moderate	SGLT2 inhibitors were more effective than placebo at reducing the risk of worsening composite kidney outcomes
Stroke	HR 0.98 (95% CI, 0.86 to 1.11); p<0.00001	High	There was no difference between SGLT2 inhibitors and placebo in the risk of stroke

Limitations to the review included no assessment of publication bias due to the inclusion of less than 10 trials, assessment of risk of bias but rated all domains as low, which suggests potential bias since critical evaluation of the literature seldom results in these findings.

After review, 25 systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[14–23, 24–33, 34–38]

New Guidelines:
High Quality Guidelines:
No new high quality guidelines were identified.

Additional Guidelines for Clinical Context:

ADA – Standards in Medical Care 2021
In 2021 the American Diabetes Association (ADA) updated guidance on the treatment of patients with T2D.[39] Due to lack of details on guideline methodology and a significant portion of the professional practice committee members having conflicts of interest with industry, the standards will not be reviewed in detail or relied upon for policy making decisions. The recommendations will be presented for clinical context. Recommendations were graded according to the evidence, ranging from level A (clear evidence based on RCTs), B (evidence from well conducted cohort studies), C (evidence from poorly controlled or uncontrolled trials) to E (expert consensus or clinical opinion).

Recommendations for the pharmacologic treatment of patients with T2D are presented in **Table 4**.[39] Pharmacotherapy should be initiated via a patient-centered approach to guide treatment selection. Metformin should be continued long-term and combined with additional therapies, including insulin, if needed. Metformin, used for glucose lowering, can be continued in patients with stable HF if eGFR remains >30 mL/min/1.73m^2. Metformin should not be used in patients who are unstable or hospitalized with heart failure. Medications should be re-evaluated every 3-6 months.

Table 4. ADA Pharmacotherapy Recommendations for Patients with Type 2 Diabetes[39]

Pharmacotherapy	Recommendation	Evidence Level
Metformin	- Preferred initial pharmacologic agent	A
Combination therapy	- Early initiation should be considered to extend time to treatment failure	A
Insulin	- Should be initiated if evidence of ongoing catabolism (weight loss), symptoms of hyperglycemia are present or when A1C levels (>10 %) or blood glucose levels (≥300 mg/dL) are very high	E
SGLT2 Inhibitors*	- Recommended for patients with established atherosclerotic CV disease or indicators of high risk, established kidney disease, or heart failure independent of A1C and in consideration of patient-specific factors. - Recommended for patients with established atherosclerotic CV disease, multiple atherosclerotic CV disease risk factors, or diabetic kidney disease to reduce the risk of major CV events and/or HF hospitalization	A

	- Recommended for patients with established HF with reduced ejection fraction is recommended to reduce the risk of worsening heart failure and CV death - Recommended for patients who have diabetic kidney disease for CV risk reduction when eGFR and urinary albumin creatinine are $\geq$ 30 mL/min/1.73m^2 or > 300 mg/g, respectively	
GLP-1 RAs*	- Recommended over insulin when possible - Recommended for patients with established atherosclerotic CV disease or indicators of high risk, established kidney disease, or heart failure independent of A1C and in consideration of patient-specific factors - Recommended for patients with established atherosclerotic CV disease or multiple atherosclerotic CV disease risk factors to reduce risk of major adverse CV events - Recommended for patients with CKD who are increased risk of CV events to reduce renal endpoints, primarily albuminuria, progression of albuminuria and CV events7	A
Abbreviations: CV – cardiovascular; eGFR – estimated glomerular filtration rate; GLP-1 RAs – glucagon-like peptide 1 receptor agonists; HF – heart failure; SGLT -2 – sodium glucose cotransporter-2 Key: * Select therapies with CV benefit (canagliflozin, dapagliflozin, empagliflozin, liraglutide, semaglutide, albiglutide, and dulaglutide)		

KDIGO – Diabetes Management in Chronic Kidney Disease

A 2020 update of the KDIGO guidelines for the management of patients with chronic kidney disease was published. Guideline methodology was clearly described and guideline development was patterned off of the AGREE II Checklist.[40] Chairs and working group members had conflicts of interest and the organization is funded by corporate sponsors so recommendations will be provided for clinical context. Recommendations were graded with a strength of recommendation and quality supporting evidence (**Table 5**). In addition to recommendations that are based on a systematic review and grading of the evidence, the guideline also includes "practice points" which are based on expert opinion.

Table 5. Description of KDIGO Recommendation Grading and Quality of Evidence Description[40]

NOMENCLATURE AND DESCRIPTION FOR RATING GUIDELINE RECOMMENDATIONS

Within each recommendation, the strength of the recommendation is indicated as **Level 1** or **Level 2**, and the quality of the supporting evidence is shown as **A**, **B**, **C**, or **D**.

	Implications		
Grade	**Patients**	**Clinicians**	**Policy**
Level 1 "We recommend"	Most people in your situation would want the recommended course of action, and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2 "We suggest"	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

Grade	**Quality of evidence**	**Meaning**
A	High	We are confident that the true effect is close to the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of effect is very uncertain, and often it will be far from the true effect.

Recommendations for glucose-lowering drugs are presented in **Table 6**.[40] Patients with T2D and CKD are candidates for treatment with metformin and a SGLT2 inhibitor, with metformin recommended first-line in patients that are treatment naïve. In patients taking metformin, the eGFR should monitored and if the eGFR is < 45 ml/min per 1.73 m^2 the dose should be divided in half (e.g., 500 mg twice daily). Patients with certain risk factors and an eGFR of 45-59 ml/min per 1.73 m^2 may be candidates for dose reduction. Patients receiving metformin for more than 4 years are at increased risk of vitamin B12 deficiency and should be monitored. Kidney function should be monitored annually and every 3-6 months in patients with an eGFR or 59 ml/min per 1.73 m^2 or less. SGLT2 inhibitors are recommended in preference to other glucose-lowering therapies besides metformin. Preference should be given to SGLT2 inhibitor with kidney or CV benefit. SGLT2 inhibitors can cause hypovolemia and ketosis and consideration should be given to discontinuing diuretics and temporary holding therapy in patients undergoing surgery, during prolonged fasting or with critically illness. Use of SGLT2 inhibitors should not occur in patients with kidney transplant. Choice of GLP-1 RA should be based on therapies with documented CV benefit. If exenatide is used, the patient should have a minimum CrCl of 30 ml/min.

Table 6. KIDGO Recommendations for Patients with Diabetes and Chronic Kidney Disease[40]

Recommendation	Strength of Recommendations	Quality of Evidence
Treat patients with T2D, CKD and an eGFR ≥30 ml/min per 1.73 m^2 with metformin	Level 1	B
Treat patients with T2D, CKD and an eGFR ≥30 ml/min per 1.73 m^2 with SGLT-2 inhibitors	Level 1	A
Patients not meeting glycemic targets with T2D, CKD taking metformin and an SGLT2 inhibitor, or who are not ablet to take them, long-acting GLP-1 RAs are recommended	Level 1	B
Abbreviations: CKD – chronic kidney disease; CrCl – creatinine clearance; eGFR – estimated glomerular filtration rate; SGLT-2 – sodium-glucose cotransporter-2; T2D – type 2 diabetes;		

After review, no guidelines were excluded due to poor quality.

New Formulations or Indications:

Dapagliflozin (Farxiga) – In April of 2021, dapagliflozin received an additional indication to reduce the risk of sustained eGFR decline, end-state kidney disease, CV death and hospitalization for HF in adults with chronic kidney disease at risk of progression (**Table 8** – DAPA-CKD).[7,11]

Dapagliflozin was also approved to reduce the risk of CV death and hospitalization for HF in adults with HF (NYHA class II-IV) with reduced ejection fraction in May of 2020 (**Table 8** – DAPA-HF).[6,11]

New FDA Safety Alerts:

Table 7. Description of new FDA Safety Alerts[8]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Canagliflozin*	INVOKANA	8/18/2020	Boxed Warning	Removal of warning for lower limb amputation and the removal of the albuminuria condition for continued dosing of patients whose eGFR falls between 30 and less than 45 mL/min/1.73 m^2
Canagliflozin*	INVOKANA	3/19/2020	Warnings and Precautions	Canagliflozin should be stopped at least 3 days prior to surgery to reduce the risk of developing ketoacidosis after surgery
Dapagliflozin*	FARXIGA	3/19/2020	Warnings and Precautions	Dapagliflozin should be stopped at least 3 days prior to surgery to reduce the risk of developing ketoacidosis after surgery
Empagliflozin*	JARDIANCE	3/19/2020	Warnings and Precautions	Empagliflozin should be stopped at least 3 days prior to surgery to reduce the risk of developing ketoacidosis after surgery
Ertugliflozin	STEGLATRO	3/19/2020	Warnings and Precautions	Ertugliflozin should be stopped at least 4 days prior to surgery to reduce the risk of developing ketoacidosis after surgery

Key: * Also applies to combination products

Randomized Controlled Trials:
A total of 34 citations were manually reviewed from the initial literature search. After further review, 29 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining 5 trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 8. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Packer, et al[3] (EMPEROR-Reduced) MC, DB, PC, RCT, Phase 3 Median follow-up: 16 months	Empagliflozin 10 mg orally daily Vs. Placebo N = 3730	Patients with class, II, III, or IV HF and an ejection fraction of 40% or less	Composite endpoint of CV death or hospitalization for worsening heart failure	Empagliflozin: 361 (19.4%) Placebo: 462 (24.7%) HR 0.75 (95% CI, 0.65 to 0.86) P<0.001 ARR 5.3%/NNT 19 *Empagliflozin was more effective than placebo at reducing CV death or hospitalization for HF in patients with and without diabetes*
Cannon, et al[4] MC, DB, PC, NI, RCT, Phase 3 (VERTIS-CV) Mean follow-up: 3.5 years	Ertugliflozin 5 mg* orally once daily OR Ertugliflozin 15 mg* orally once daily OR Placebo orally once daily	Patients with T2DM and atherosclerotic CV disease N = 8246	Major CV events (composite of death from CV causes, nonfatal myocardial infarction or nonfatal stroke) Noninferiority margin was 1.3	Ertugliflozin: 653 (11.9%) Placebo: 327 (11.9%) HR 0.97; 95.6% CI, 0.85 to 1.11 P<0.001 for noninferiority *Ertugliflozin did not reduce or increase the risk of major CV events compared to placebo.*
Heerspink, et al[5] (DAPA-CKD) MC, DB, PC, RCT, Phase 3 Mean follow-up: 2.4 years	Dapagliflozin 10 mg orally once daily Vs. Placebo	Patients with CKD, with or without T2DM N = 4304	Composite of sustained decline in the estimated eGFR of at least 50%, end-stage kidney disease or death from renal or CV disease	Dapagliflozin: 197 (9.2%) Placebo: 312 (14.5%) HR 0.61 (95% CI, 0.51 to 0.72) P<0.001 ARR 5.3% / NNT 19 *Dapagliflozin was more effective than placebo at reducing the risk of progression of CKD in patients with and without diabetes*

McMurray, et al[6] (DAPA-HF) MC, DB, PC, RCT, Phase 3 Median follow-up: 18.2 months	Dapagliflozin 10 mg orally once daily Vs. Placebo * On standard heart failure drug therapy	Patients with NY Heart Association class II, III, or IV heart failure and an ejection fraction of 40% or less * 42% with diabetes N = 4744	Composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or CV death	Dapagliflozin: 386 (16.3%) Placebo: 502 (21.2%) HR 0.74 (95% CI, 0.65 to 0.85) P<0.001 ARR 4.9%/NNT 21 *Dapagliflozin was more effective than placebo at reducing the risk of worsening heart failure or death from CV causes in patients with and without diabetes*
Perkovic, et al[7] (CREDENCE) MC, DB, PC, RCT, Phase 3 Mean follow-up: 2.62 years	Canagliflozin 100 mg orally daily Vs. Placebo	Patients with T2D and albuminuric chronic kidney disease N = 4401	Composite of end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of <15 mL per minute per 1.73 m^2), doubling of serum creatinine level, or death from renal or CV causes	Canagliflozin: 245 (11%) Placebo: 340 (14%) HR 0.70 (95% CI, 0.59 to 0.82) P = 0.00001 *Canagliflozin reduced the risk of kidney failure and CV events more than placebo, 43.2 events per 1000 patient-years compared to 61.2 events per 1000 patient years, respectively, in patients with T2D and kidney disease*

Key: * Pooled results

Abbreviations: ARR = absolute risk reduction; CV = cardiovascular; DB = double-blind, GFR = glomerular filtration rate; HR = hazard ratio; MC = multi-center; NI = noninferiority; NNT = number needed to treat; NY = New York; PC = placebo controlled; RCT = randomized clinical trial; T2D = type 2 diabetes mellitus

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
canagliflozin	INVOKANA	TABLET	Y
dapagliflozin propanediol	FARXIGA	TABLET	Y
empagliflozin	JARDIANCE	TABLET	Y
canagliflozin/metformin HCl	INVOKAMET XR	TAB BP 24H	N
canagliflozin/metformin HCl	INVOKAMET	TABLET	N
dapagliflozin/metformin HCl	XIGDUO XR	TAB BP 24H	N
dapagliflozin/saxagliptin HCl	QTERN	TABLET	N
empaglifloz/linaglip/metformin	TRIJARDY XR	TAB BP 24H	N
empagliflozin/linagliptin	GLYXAMBI	TABLET	N
empagliflozin/metformin HCl	SYNJARDY XR	TAB BP 24H	N
empagliflozin/metformin HCl	SYNJARDY	TABLET	N
ertugliflozin pidolate	STEGLATRO	TABLET	N
ertugliflozin/metformin	SEGLUROMET	TABLET	N
ertugliflozin/sitagliptin	STEGLUJAN	TABLET	N

Appendix 2: Abstracts of Comparative Clinical Trials

Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes

Richard Pratley , Samuel Dagogo-Jack , James Mancuso , Susan Huyck , Urszula Masiukiewicz , Bernard Charbonnel , Robert Frederich , Silvina Gallo, Francesco Cosentino, Weichung J Shih, Ira Gantz, Steven G Terra, David Z I Cherney, Darren K McGuire, VERTIS CV Investigators

Background: The cardiovascular effects of ertugliflozin, an inhibitor of sodium-glucose cotransporter 2, have not been established.

Methods: In a multicenter, double-blind trial, we randomly assigned patients with type 2 diabetes and atherosclerotic cardiovascular disease to receive 5 mg or 15 mg of ertugliflozin or placebo once daily. With the data from the two ertugliflozin dose groups pooled for analysis, the primary objective was to show the noninferiority of ertugliflozin to placebo with respect to the primary outcome, major adverse cardiovascular events (a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke). The noninferiority margin was 1.3 (upper boundary of a 95.6% confidence interval for the hazard ratio [ertugliflozin vs. placebo] for major adverse cardiovascular events). The first key secondary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure.

Results: A total of 8246 patients underwent randomization and were followed for a mean of 3.5 years. Among 8238 patients who received at least one dose of ertugliflozin or placebo, a major adverse cardiovascular event occurred in 653 of 5493 patients (11.9%) in the ertugliflozin group and in 327 of 2745 patients (11.9%) in the placebo group (hazard ratio, 0.97; 95.6% confidence interval [CI], 0.85 to 1.11; P<0.001 for noninferiority). Death from cardiovascular causes or hospitalization for heart failure occurred in 444 of 5499 patients (8.1%) in the ertugliflozin group and in 250 of 2747 patients (9.1%) in the placebo group (hazard ratio, 0.88; 95.8% CI, 0.75 to 1.03; P = 0.11 for superiority). The hazard ratio for death from cardiovascular causes was 0.92 (95.8% CI, 0.77 to 1.11), and the hazard ratio for death from renal causes, renal replacement therapy, or doubling of the serum creatinine level was 0.81 (95.8% CI, 0.63 to 1.04). Amputations were performed in 54 patients (2.0%) who received the 5-mg dose of ertugliflozin and in 57 patients (2.1%) who received the 15-mg dose, as compared with 45 patients (1.6%) who received placebo.

Conclusions: Among patients with type 2 diabetes and atherosclerotic cardiovascular disease, ertugliflozin was noninferior to placebo with respect to major adverse cardiovascular events. (Funded by Merck Sharp & Dohme and Pfizer; VERTIS CV ClinicalTrials.gov number, NCT01986881.).

Dapagliflozin in Patients with Chronic Kidney Disease

Hiddo J L Heerspink, Bergur V Stefánsson, Ricardo Correa-Rotter, Glenn M Chertow, Tom Greene, Fan-Fan Hou, Johannes F E Mann, John J V McMurray , Magnus Lindberg, Peter Rossing, C David Sjöström, Roberto D Toto, Anna-Maria Langkilde, David C Wheeler, DAPA-CKD Trial Committees and Investigators

Background: Patients with chronic kidney disease have a high risk of adverse kidney and cardiovascular outcomes. The effect of dapagliflozin in patients with chronic kidney disease, with or without type 2 diabetes, is not known.

Methods: We randomly assigned 4304 participants with an estimated glomerular filtration rate (GFR) of 25 to 75 ml per minute per 1.73 m^2 of body-surface area and a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of 200 to 5000 to receive dapagliflozin (10 mg once daily) or placebo. The primary outcome was a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes.

Results: The independent data monitoring committee recommended stopping the trial because of efficacy. Over a median of 2.4 years, a primary outcome event occurred in 197 of 2152 participants (9.2%) in the dapagliflozin group and 312 of 2152 participants (14.5%) in the placebo group (hazard ratio, 0.61; 95% confidence interval [CI], 0.51 to 0.72; P<0.001; number needed to treat to prevent one primary outcome event, 19 [95% CI, 15 to 27]). The hazard ratio for the composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal causes was 0.56 (95% CI, 0.45 to 0.68; P<0.001), and the hazard ratio for the composite of death from cardiovascular causes or hospitalization for heart failure was 0.71 (95% CI, 0.55 to 0.92; P = 0.009). Death occurred in 101 participants (4.7%) in the dapagliflozin group and 146 participants (6.8%) in the placebo group (hazard ratio, 0.69; 95% CI, 0.53 to 0.88; P = 0.004). The effects of dapagliflozin were similar in participants with type 2 diabetes and in those without type 2 diabetes. The known safety profile of dapagliflozin was confirmed.

Conclusions: Among patients with chronic kidney disease, regardless of the presence or absence of diabetes, the risk of a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes was significantly lower with dapagliflozin than with placebo. (Funded by AstraZeneca; DAPA-CKD ClinicalTrials.gov number, NCT03036150.).

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

John J V McMurray, Scott D Solomon, Silvio E Inzucchi, Lars Køber, Mikhail N Kosiborod, Felipe A Martinez, Piotr Ponikowski, Marc S Sabatine, Inder S Anand , Jan Bělohlávek , Michael Böhm , Chern-En Chiang , Vijay K Chopra , Rudolf A de Boer , Akshay S Desai , Mirta Diez , Jaroslaw Drozdz , Andrej Dukát , Junbo Ge , Jonathan G Howlett , Tzvetana Katova , Masafumi Kitakaze , Charlotta E A Ljungman , Béla Merkely, Jose C Nicolau, Eileen O'Meara, Mark C Petrie, Pham N Vinh, Morten Schou, Sergey Tereshchenko, Subodh Verma, Claes Held, David L DeMets , Kieran F Docherty, Pardeep S Jhund, Olof Bengtsson, Mikaela Sjöstrand, Anna-Maria Langkilde , DAPA-HF Trial Committees and Investigators

Background: In patients with type 2 diabetes, inhibitors of sodium-glucose cotransporter 2 (SGLT2) reduce the risk of a first hospitalization for heart failure, possibly through glucose-independent mechanisms. More data are needed regarding the effects of SGLT2 inhibitors in patients with established heart failure and a reduced ejection fraction, regardless of the presence or absence of type 2 diabetes.

Methods: In this phase 3, placebo-controlled trial, we randomly assigned 4744 patients with New York Heart Association class II, III, or IV heart failure and an ejection fraction of 40% or less to receive either dapagliflozin (at a dose of 10 mg once daily) or placebo, in addition to recommended therapy. The primary outcome was a composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or cardiovascular death.

Results: Over a median of 18.2 months, the primary outcome occurred in 386 of 2373 patients (16.3%) in the dapagliflozin group and in 502 of 2371 patients (21.2%) in the placebo group (hazard ratio, 0.74; 95% confidence interval [CI], 0.65 to 0.85; P<0.001). A first worsening heart failure event occurred in 237 patients (10.0%) in the dapagliflozin group and in 326 patients (13.7%) in the placebo group (hazard ratio, 0.70; 95% CI, 0.59 to 0.83). Death from cardiovascular

causes occurred in 227 patients (9.6%) in the dapagliflozin group and in 273 patients (11.5%) in the placebo group (hazard ratio, 0.82; 95% CI, 0.69 to 0.98); 276 patients (11.6%) and 329 patients (13.9%), respectively, died from any cause (hazard ratio, 0.83; 95% CI, 0.71 to 0.97). Findings in patients with diabetes were similar to those in patients without diabetes. The frequency of adverse events related to volume depletion, renal dysfunction, and hypoglycemia did not differ between treatment groups.

Conclusions: Among patients with heart failure and a reduced ejection fraction, the risk of worsening heart failure or death from cardiovascular causes was lower among those who received dapagliflozin than among those who received placebo, regardless of the presence or absence of diabetes. (Funded by AstraZeneca; DAPA-HF ClinicalTrials.gov number, NCT03036124.).

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

Milton Packer [1], Stefan D Anker [1], Javed Butler [1], Gerasimos Filippatos [1], Stuart J Pocock [1], Peter Carson [1], James Januzzi [1], Subodh Verma [1], Hiroyuki Tsutsui [1], Martina Brueckmann [1], Waheed Jamal [1], Karen Kimura [1], Janet Schnee [1], Cordula Zeller [1], Daniel Cotton [1], Edimar Bocchi [1], Michael Böhm [1], Dong-Ju Choi [1], Vijay Chopra [1], Eduardo Chuquiure [1], Nadia Giannetti [1], Stefan Janssens [1], Jian Zhang [1], Jose R Gonzalez Juanatey [1], Sanjay Kaul [1], Hans-Peter Brunner-La Rocca [1], Bela Merkely [1], Stephen J Nicholls [1], Sergio Perrone [1], Ileana Pina [1], Piotr Ponikowski [1], Naveed Sattar [1], Michele Senni [1], Marie-France Seronde [1], Jindrich Spinar [1], Iain Squire [1], Stefano Taddei [1], Christoph Wanner [1], Faiez Zannad [1], EMPEROR-Reduced Trial Investigators

Background: Sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of hospitalization for heart failure in patients regardless of the presence or absence of diabetes. More evidence is needed regarding the effects of these drugs in patients across the broad spectrum of heart failure, including those with a markedly reduced ejection fraction.

Methods: In this double-blind trial, we randomly assigned 3730 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less to receive empagliflozin (10 mg once daily) or placebo, in addition to recommended therapy. The primary outcome was a composite of cardiovascular death or hospitalization for worsening heart failure.

Results: During a median of 16 months, a primary outcome event occurred in 361 of 1863 patients (19.4%) in the empagliflozin group and in 462 of 1867 patients (24.7%) in the placebo group (hazard ratio for cardiovascular death or hospitalization for heart failure, 0.75; 95% confidence interval [CI], 0.65 to 0.86; P<0.001). The effect of empagliflozin on the primary outcome was consistent in patients regardless of the presence or absence of diabetes. The total number of hospitalizations for heart failure was lower in the empagliflozin group than in the placebo group (hazard ratio, 0.70; 95% CI, 0.58 to 0.85; P<0.001). The annual rate of decline in the estimated glomerular filtration rate was slower in the empagliflozin group than in the placebo group (-0.55 vs. -2.28 ml per minute per 1.73 m^2 of body-surface area per year, P<0.001), and empagliflozin-treated patients had a lower risk of serious renal outcomes. Uncomplicated genital tract infection was reported more frequently with empagliflozin.

Conclusions: Among patients receiving recommended therapy for heart failure, those in the empagliflozin group had a lower risk of cardiovascular death or hospitalization for heart failure than those in the placebo group, regardless of the presence or absence of diabetes. (Funded by Boehringer Ingelheim and Eli Lilly; EMPEROR-Reduced ClinicalTrials.gov number, NCT03057977.).

Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

Vlado Perkovic [1], Meg J Jardine [1], Bruce Neal [1], Severine Bompoint [1], Hiddo J L Heerspink [1], David M Charytan [1], Robert Edwards [1], Rajiv Agarwal [1], George Bakris [1], Scott Bull [1], Christopher P Cannon [1], George Capuano [1], Pei-Ling Chu [1], Dick de Zeeuw [1], Tom Greene [1], Adeera Levin [1], Carol Pollock [1], David C Wheeler [1], Yshai Yavin [1], Hong Zhang [1], Bernard Zinman [1], Gary Meininger [1], Barry M Brenner [1], Kenneth W Mahaffey [1], CREDENCE Trial Investigators

Background: Type 2 diabetes mellitus is the leading cause of kidney failure worldwide, but few effective long-term treatments are available. In cardiovascular trials of inhibitors of sodium-glucose cotransporter 2 (SGLT2), exploratory results have suggested that such drugs may improve renal outcomes in patients with type 2 diabetes.
Methods: In this double-blind, randomized trial, we assigned patients with type 2 diabetes and albuminuric chronic kidney disease to receive canagliflozin, an oral SGLT2 inhibitor, at a dose of 100 mg daily or placebo. All the patients had an estimated glomerular filtration rate (GFR) of 30 to <90 ml per minute per 1.73 m^2 of body-surface area and albuminuria (ratio of albumin [mg] to creatinine [g], >300 to 5000) and were treated with renin-angiotensin system blockade. The primary outcome was a composite of end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of <15 ml per minute per 1.73 m^2), a doubling of the serum creatinine level, or death from renal or cardiovascular causes. Prespecified secondary outcomes were tested hierarchically.
Results: The trial was stopped early after a planned interim analysis on the recommendation of the data and safety monitoring committee. At that time, 4401 patients had undergone randomization, with a median follow-up of 2.62 years. The relative risk of the primary outcome was 30% lower in the canagliflozin group than in the placebo group, with event rates of 43.2 and 61.2 per 1000 patient-years, respectively (hazard ratio, 0.70; 95% confidence interval [CI], 0.59 to 0.82; P = 0.00001). The relative risk of the renal-specific composite of end-stage kidney disease, a doubling of the creatinine level, or death from renal causes was lower by 34% (hazard ratio, 0.66; 95% CI, 0.53 to 0.81; P<0.001), and the relative risk of end-stage kidney disease was lower by 32% (hazard ratio, 0.68; 95% CI, 0.54 to 0.86; P = 0.002). The canagliflozin group also had a lower risk of cardiovascular death, myocardial infarction, or stroke (hazard ratio, 0.80; 95% CI, 0.67 to 0.95; P = 0.01) and hospitalization for heart failure (hazard ratio, 0.61; 95% CI, 0.47 to 0.80; P<0.001). There were no significant differences in rates of amputation or fracture.
Conclusions: In patients with type 2 diabetes and kidney disease, the risk of kidney failure and cardiovascular events was lower in the canagliflozin group than in the placebo group at a median follow-up of 2.62 years. (Funded by Janssen Research and Development; CREDENCE ClinicalTrials.gov number, NCT02065791.).

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to May 17, 2021
Search Strategy:

#	Searches	Results
1	canagliflozin.mp. or Canagliflozin/	1344
2	dapagliflozin.mp.	1643
3	empagliflozin.mp.	1683
4	ertugliflozin.mp.	150
5	1 or 2 or 3 or 4	3720
6	limit 5 to (english language and humans and yr="2020 -Current")	383
7	limit 6 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	34

Appendix 4: Key Inclusion Criteria

Population	Patients with type 2 diabetes mellitus
Intervention	SGLT-2 inhibitors
Comparator	Placebo or active control
Outcomes	A1C, mortality, hospitalizations, reductions in CV or CKD risk
Setting	Outpatient

Sodium-Glucose Cotransporter-2 Inhibitors (SGLT-2 Inhibitors)

Goal(s):
- Promote cost-effective and safe step-therapy for management of type 2 diabetes mellitus (T2DM).

Length of Authorization:
- Up to 12 months

Requires PA:
- All SGLT-2 inhibitors

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. Approved Indications for SGLT2 Inhibitors (in addition to glucose lowering)

Drug Name	CV risk reduction in patients with T2D and established CV disease	Reduction in risk of end-stage kidney disease in patients with T2D and diabetic nephropathy with albuminuria >300 mg/day	Reduction in risk of eGFR decline and end-stage kidney disease CV death and hospitalization for HF in patients with CKD at risk of progression	HF risk reduction in patients with T2D and established CV disease or multiple CV risk factors	HF risk reduction in patients with HF and HFrEF
Canagliflozin	X	X			
Dapagliflozin			X	X	X
Empagliflozin	X				
Ertugliflozin					

Abbreviations: CKD – chronic kidney disease; CV – cardiovascular; eGFR – estimated glomerular filtration rate; HF – heart failure; HFrEF – heart failure with reduced ejection fraction; T2D – type 2 diabetes

Approval Criteria		
1. Is this a request for renewal of a previously approved prior authorization?	**Yes:** Go the **Renewal Criteria**	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code	
3. Does the patient qualify for the requested therapy based on diagnoses and requirements in Table 1?	**Yes:** Go to #5	**No:** Go to #4
4. Does the patient have T2D and failed, or have contraindications to, metformin or is requesting a SGLT2 inhibitor to be used in combination with metformin? (document contraindication, if any)	**Yes:** Go to #5	**No:** Pass to RPh. Deny and recommend trial of metformin. See below for metformin titration schedule.
5. Is the request for a SGLT2 inhibitor (including combination products) and there is a documented estimated glomerular filtration rate (eGFR) showing the product is not contraindicated? Products listed below should not be used in the following patients: • Canagliflozin and on dialysis, or • Empagliflozin and on dialysis , or • Dapagliflozin and eGFR on dialysis, or • Ertugliflozin and eGFR <30 mL/min/ 1.73 m^2?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is the request for the renewal of a SGLT2 inhibitor (including combination products) and there is a documented eGFR showing the product is not contraindicated? : Products listed below should not be used in the following patients: • Canagliflozin and on dialysis, or • Empagliflozin and on dialysis, or • Dapagliflozin and on dialysis, or • Ertugliflozin and eGFR <30 mL/min/ 1.73 m^2?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Initiating Metformin

1.	Begin with low-dose metformin (500 mg) taken once or twice per day with meals (breakfast and/or dinner) or 850 mg once per day.
2.	After 5-7 days, if gastrointestinal side effects have not occurred, advance dose to 850 mg, or two 500 mg tablets, twice per day (medication to be taken before breakfast and/or dinner).
3.	If gastrointestinal side effects appear with increasing doses, decrease to previous lower dose and try to advance the dose at a later time.
4.	The maximum effective dose can be up to 1,000 mg twice per day but is often 850 mg twice per day. Modestly greater effectiveness has been observed with doses up to about 2,500 mg/day. Gastrointestinal side effects may limit the dose that can be used.

Nathan, et al. Medical management of hyperglycemia in Type 2 Diabetes: a consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care*. 2008; 31;1-11.

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