

## Class Update: Sodium-glucose Cotransporter 2 (SGLT2) Inhibitors

**Date of Review:** March 2016

**Date of Last Review:** September 2015

### **Current Status of PDL Class:**

See **Appendix 1**.

### **Purpose for Class Update:**

The sodium-glucose cotransporter 2 (SGLT2) inhibitor class was updated in September as part of the non-insulin antidiabetic agent class review. However, new evidence on the cardiovascular (CV) effects of the SGLT2 inhibitor empagliflozin has become available. The goal of this review is to evaluate updated evidence for SGLT2 inhibitors and determine if changes related to current prior authorization (PA) criteria the Oregon Health Plan (OHP) Preferred Drug List (PDL) are needed.

### **Research Questions:**

1. Is there any new comparative evidence for SGLT2 inhibitors pertaining to CV benefits or other clinically relevant outcomes (e.g. microvascular, macrovascular and mortality outcomes)?
2. Is there any new evidence of comparative harms between SGLT2 inhibitors and other non-insulin antidiabetic treatments?
3. Are there subgroups of patients with type 2 diabetes (T2DM) in which SGLT2 inhibitors may be more effective or associated with less harm?

### **Conclusions:**

- One industry-funded, multinational, randomized controlled trial and two Food and Drug Administration (FDA) safety updates have been published since the last review. There are no new systematic reviews or guidelines.<sup>1,2</sup>
- In patients with a history of CV disease, there was moderate strength of evidence that empagliflozin (pooled data from 10 mg and 25 mg doses) decreased the primary composite CV endpoint of CV death, non-fatal myocardial infarction (MI), or non-fatal stroke versus placebo (10.5% vs. 12.1%), with a number needed to treat (NNT) of 63 over 3.1 years (hazard ratio [HR] 0.86; 95.02% CI, 0.74 to 0.99; P<0.001 for noninferiority; P=0.04 for superiority).<sup>1</sup> Reduction in the primary endpoint was driven by a statistically significant 2.2% reduction in CV death (3.7% vs. 5.9%).<sup>1</sup> There were no statistically significant differences between empagliflozin and placebo in incidence of non-fatal MI or non-fatal stroke.<sup>1</sup>
- There was a statistically significant reduction in death from any cause with empagliflozin compared to placebo (5.7% vs. 8.3%; HR 0.68; 95% CI, 0.57 to 0.82; P<0.001).<sup>1</sup>
- The CV benefit may be from the diuretic effect of empagliflozin. This theory is supported by the reduction in hospitalizations related to heart failure found in the empagliflozin group compared to placebo (4.1% vs. 2.7% [HR 0.65; 95% CI, 0.50 to 0.85]; P=0.002).<sup>1</sup>
- No dose-response with empagliflozin was found; therefore, the 10 mg dose is recommended for most patients. Seventy-eight percent of patients were on additional antidiabetic therapy, the most common drugs being metformin (74%), insulin (48%) and sulfonylureas (43%).<sup>1</sup>

- There is insufficient evidence to determine whether the same risk reduction would be seen in T2DM patients *without* preexisting CV disease. A systematic review and meta-analysis of dapagliflozin and canagliflozin studies demonstrated inconclusive findings on the effect of SGLT2 inhibitors on CV outcomes (OR 0.89; 95% CI, 0.70 to 1.14).<sup>4</sup> Results from ongoing studies with canagliflozin and dapagliflozin will help to determine if the results seen with empagliflozin trial is a consistent class effect of SGLT2 inhibitors or if it is unique to empagliflozin.<sup>5,6</sup>
- There was a non-statistically significant increase in the rate of nonfatal strokes in empagliflozin-treated patients, which warrants further investigation.<sup>1</sup> An FDA analysis reported higher incidence of nonfatal stroke with canagliflozin, another SGLT2 inhibitor, compared to controls (HR 1.46; 95% CI 0.83 to 2.58).<sup>4</sup> Canagliflozin has also been associated with increased rates of bone fractures. The long-term effect of SGLT2 inhibitors on bone density is still unknown.<sup>2</sup>
- There is high strength evidence that genital mycotic infections are more common in females and males who take SGLT2 inhibitors, which was again seen in the empagliflozin trial with an incidence of 6.4% compared to 1.8% for placebo (p<0.001).<sup>1,4</sup>
- SGLT2 inhibitors are considered one of many second-line treatment options for T2DM by the American Diabetes Association (ADA).<sup>7</sup> The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) recommends them as an option for patients presenting with all levels of A1C.<sup>8,9</sup> However, these recommendations are informed by opinions of the guideline writers and not based on comparative safety or efficacy data. The National Institute for Health and Care Excellence (NICE), which also factors in cost-effectiveness, recommends empagliflozin or canagliflozin as a third-line option in patients already taking metformin and a SU, unless a sulfonylurea (SU) is contraindicated.<sup>10,11</sup>

#### **Recommendations:**

- No changes to the current clinical PA criteria or Preferred Drug List (PDL) recommended. Due to safety concerns with use of SGLT2 inhibitors, more data are needed to determine their place in therapy.

#### **Previous Conclusions:**

- There is insufficient new comparative evidence for efficacy/effectiveness on differences of microvascular outcomes (retinopathy, nephropathy and neuropathy) between different treatments for type 2 diabetes mellitus (T2DM).<sup>12</sup> Evidence-based recommendations in new clinical practice guidelines from the American Diabetes Association (ADA), Institute for Clinical Systems Improvement (ICIS), and the National Institute for Health and Care Excellence (NICE), American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) and a systematic review draft report from the Agency for Healthcare Research and Quality (AHRQ), support the current status of non-insulin antidiabetic therapies on the preferred drug list (PDL).<sup>12</sup>
- High quality evidence suggest patients on metformin, pioglitazone, metformin plus a dipeptidyl peptidase-4 (DPP-4) inhibitor, or metformin plus a SGLT-2 inhibitor have similar rates of all-cause mortality, based on one systematic review.<sup>12</sup>
- There is high quality evidence that monotherapy with either metformin, a thiazolidinedione (TZD) or a sulfonylurea (SU) results in similar lowering of A1C based on one systematic review.<sup>12</sup>
- There is moderate quality evidence that DPP-4 inhibitors lower A1C less than metformin and glimepiride based on two systematic reviews (one for each comparison).<sup>12</sup>
- Moderate quality evidence, from one fair and one good quality trial, suggests that DPP-4 inhibitors do not reduce major CV outcomes compared to placebo.<sup>12</sup> Data from the EXAMINE and TECOS found these drugs to be non-inferior to placebo when a composite of CV outcomes were evaluated.<sup>12</sup>
- Moderate quality evidence from two meta-analyses showed a statistically significant increase in HF outcomes with DPP-4 inhibitors compared to placebo or active treatment.<sup>12</sup> Studies included in the meta-analyses were of short duration and the majority of included outcomes were limited to 2 trials only [SAVORTIMI53 (saxagliptin) and EXAMINE (alogliptin)].<sup>12</sup>
- High quality evidence suggest hypoglycemia rates are higher with SU than comparative T2DM therapy based on two systematic reviews.<sup>12</sup>

- Evidence from a recent systematic review and meta-analysis found glyburide to be associated with at least one episode of hypoglycemia compared to secretagogues [relative risk (RR) 1.52, 95% CI 1.21 to 1.92] and compared to other SUs (RR 1.83, 95% CI 1.35 to 2.49).<sup>12</sup>
- There is low quality evidence to recommend metformin use in patients with mild to moderate kidney disease based on one systematic review. Evidence from this review suggests metformin is safe in patients with mild to moderate chronic kidney disease (eGFR >30-60 mL/min per 1.73m<sup>2</sup>) without increased risk of lactic acidosis, based on evidence from primarily non-clinical trial data. The frequency of lactic acidosis in the setting of metformin therapy is very low and numerically similar to what appears to be the background rate in the population with T2DM.<sup>12</sup>
- In December of 2014 liraglutide injection (Saxenda) was approved for chronic weight management in addition to a reduced-calorie diet and physical activity. Treatments for weight loss are not funded by the OHP.<sup>12</sup>

#### **Previous Recommendations:**

- Make exenatide (Byetta®) a preferred agent but subject to current prior authorization (PA) for GLP1 receptor antagonists.
- Make empagliflozin/linagliptin (Glyxambi®) non-preferred drug subject to current PA for SGLT-2 inhibitors.
- Reorganize PDL classes for non-insulin antidiabetic agents to the following:
  - DPP-4 Inhibitors
  - GLP-1 Receptor Antagonists
  - Miscellaneous Antidiabetic Agents (metformin, pramlintide, meglitinides, others).
  - SGLT-2 Inhibitors
  - Sulfonylureas
  - Thiazolidinediones
- Remove clinical PA for pramlintide due to low overall utilization and current FDA-mandated Risk Evaluation Mitigation Strategy (REMS) already in place to promote safe use through education.
- Modify SGLT-2 inhibitor clinical PA to require monitoring renal function every 6 months.
- Continue clinical PA criteria for all DPP-4 inhibitors and all GLP-1 RAs.

#### **Background:**

SGLT2 inhibitors are the newest class of antidiabetic agents for patients with T2DM. SGLT2 inhibitors increase urinary glucose excretion by decreasing renal absorption of glucose.<sup>13</sup> Because of their mechanism of action, SGLT2 inhibitors pose low risk for hypoglycemia but increase the likelihood of urinary tract and genital infections. Additional benefits of SGLT2 inhibitors are weight loss and reduced blood pressure, likely through their diuretic effect. SGLT2 inhibitors are associated with modest A1C lowering of approximately 0.5% in placebo-controlled comparisons.<sup>14</sup> There are currently three SGLT2 inhibitors available, offered as monotherapy or in combination formulations with metformin: canagliflozin (Invokana), dapagliflozin (Farxiga), and empagliflozin (Jardiance).

Cardiovascular disease is the primary complication in patients with diabetes mellitus (DM).<sup>15</sup> It is well documented that lowering A1C is associated with reduced microvascular outcomes, however the evidence for macrovascular benefits are uncertain. Additionally, some antidiabetic therapies have been associated with additional CV risk, prompting the FDA to require studies to evaluate the impact of new antidiabetic therapies on CV outcomes. Evidence suggests metformin is likely to reduce the incidence of CVD based on data from the United Kingdom Prospective Diabetes Study (UKPDS).<sup>7</sup> The TECOS trial (DPP-4 inhibitors) and ELIXA study (GLP-1 agonists) have shown a neutral impact on CV markers.<sup>16,17</sup> This review will focus on the recent evidence on the benefits of empagliflozin on CV

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outcomes. Two additional trials are underway with canagliflozin (CANVAS) and dapagliflozin (DECLARE) to determine the CV impact of these therapies.<sup>5,6</sup> These studies will provide valuable evidence on how to best manage the increased risk of CV disease seen in patients with T2DM.

**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 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, 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. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

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:**

No new systematic reviews identified.

**New Guidelines:**

No new guidelines identified.

**New Safety Alerts:**

In September 2015, the Food and Drug Administration (FDA) released a warning of an increased risk of bone fractures and decreased bone mineral density associated with the use of canagliflozin, also a SGLT2 inhibitor.<sup>2</sup> It is unknown if this is a class effect and the FDA is continuing to evaluate if other SGLT2 inhibitors convey this same risk.

The FDA released a drug safety communication in December 2015 on labeling changes for the SGLT2 inhibitor class for the risk of ketoacidosis and serious urinary tract infections, potentially leading to hospitalizations. Postmarketing studies are being required from the manufacturers of the SGLT2 inhibitors to gain additional clarity on the risk.<sup>3</sup>

**New Formulations or Indications:**

No new formulations.

**Randomized Controlled Trials:**

Twenty-three citations were manually reviewed from the literature search. After further review, 22 trials were excluded because of wrong study design (observational), comparator (placebo), outcome studied (non-clinical) or outside the search dates. The remaining trial is described below and in Table 1.

The CV effects and mortality associated with empagliflozin treatment was studied in double-blind, randomized, placebo controlled trial.<sup>1</sup> Adult patients (n=7020) with T2DM were randomized to receive a daily dose of empagliflozin 10 mg, empagliflozin 25 mg or placebo and were followed for a median 3.1 years. The median treatment duration was 2.6 years. Patients were a mean age of 63 years old, predominately male (71%), white (72%) and had a prior history of CV disease. The most common CV risk factor was coronary artery disease (CAD) (75%) followed by multi-vessel CAD (47%) and history of MI (47%). Baseline A1C levels were 8.07%. Background antidiabetic therapies were allowed.<sup>1</sup> Metformin, insulin and sulfonylureas were most commonly used with similar rates across all treatment groups. Angiotensin-converting enzyme inhibitors (ACE) or angiotensin receptor blockers (ARBs) were used by 81% of patients. Twenty-six percent of patients had moderate renal insufficiency (<60 mL/min/1.73m<sup>2</sup>).<sup>1</sup> The primary composite outcome was death from CV causes, nonfatal myocardial infarction, or nonfatal stroke. The primary outcome plus hospitalization for unstable angina was a key secondary outcome.

Patients were analyzed using a modified intention-to-treat analysis of pooled empagliflozin data versus placebo.<sup>1</sup> The noninferiority threshold for the primary outcome comparison between empagliflozin and placebo was set at a margin of 1.3 for the hazard ratio. A two-sided P value of 0.0498, or less, was used for statistical significance and the confidence interval (CI) was calculated at 95.02% for the primary outcome.

Empagliflozin (pooled data from both doses) was found to significantly lower the incidence of the composite primary outcome compared to placebo (hazard ratio [HR] 0.86; 95.02% CI, 0.74 to 0.99; p<0.001 for noninferiority and p=0.04 for superiority).<sup>1</sup> Empagliflozin was noninferior, but not statistically superior, to placebo for the key secondary composite outcome, which was the primary composite outcome plus hospitalizations for unstable angina (12.8% vs 14.4%, respectively (HR 0.89; 95% CI, 0.78 to 1.01; p<0.001 for noninferiority and p=0.08 for superiority)). When individual endpoints were analyzed, patients on empagliflozin had statistically significant lower incidence of death from CV causes, all-cause mortality, and hospitalizations for heart failure (Table 1). Rates of MI and fatal or nonfatal stroke were similar between both groups.<sup>1</sup>

Fatal or nonfatal stroke rates were higher with empagliflozin compared to placebo (HR 1.18; 95% CI, 0.89 to 1.56; p=0.26). Empagliflozin was also associated with an increased risk of nonfatal stroke (HR 1.24; 95% CI, 0.92 to 1.67; p=0.16) There was no significant difference in CV outcomes between the empagliflozin 10 mg and empagliflozin 25 mg doses. Differences in A1C reduction between the 10 mg and 25 mg doses and placebo were also similar (-0.54% [95% CI, -0.58 to -0.49] in the 10 mg group and -0.60% [95% CI, -0.64 to -0.55] in the 25 mg group).<sup>1</sup> However, by week 206 the difference had decreased to -0.24% for empagliflozin 10 mg and -0.36% for empagliflozin 25 mg, compared to placebo. Changes in CV risk factors with empagliflozin compared to placebo include reductions in the following; small changes in weight, waist circumference, uric acid levels, and systolic and diastolic blood pressure. Small increases in LDL and HDL cholesterol were seen with empagliflozin in comparison to placebo.<sup>1</sup> There was no substantial difference in A1C lowering between empagliflozin 10 mg and empagliflozin 25 mg, suggesting treatment with the 10 mg dose to be adequate for most patients.

Adverse events leading to discontinuation were lower in the pooled empagliflozin group compared to placebo, 17.3% and 19.4%, respectively.<sup>1</sup> Genital infections were the most common adverse effect associated with empagliflozin treatment, which occurred at a significantly higher rate than placebo (6.4% vs, 1.8%, respectively (p<0.001). Hypoglycemic adverse events, acute renal failure, diabetic ketoacidosis, thromboembolic events, bone fracture, symptoms of volume depletion and electrolyte changes were similar between empagliflozin and placebo.<sup>1</sup>

**Table 1. Description of Randomized Comparative Clinical Trials**

Study	Comparison	Population	N	Outcomes	ARR/N NT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability				
1. Zinman, et al (EMPA-REG OUTCOME) <sup>1</sup>  RCT, DB, DD, PG, Phase 3	1. Empagliflozin 10 mg (E10)	<u>Demographics</u> <u>(mean):</u> Age: 63 years Male: 71% White: 72% Diabetes diagnosis >10 years: 57% A1C: 8.1%	<u>ITT:</u> 1. 2345 2. 2342 3. 2333	Primary Outcome: <b>Composite of CV death, non-fatal MI, or non-fatal stroke):</b> E*: 490 (10.5%) vs. P: 282 (12.1%); HR 0.86 (95.04% CI, 0.74 to 0.99; P<0.001 for noninferiority and p=0.04 for superiority)	1.6/63	<b>D/C due to AE:</b> E*: 813 (17.3%) vs. P: 453 (19.4%); P<0.01  <b>Any hypoglycemia:</b> E*: 1303 (27.8%) vs. P: 650 (27.9%); P-value not given  <b>Genital infections:</b> E*: 301 (6.4%) vs. P: 42 (1.8%); P<0.001	2/48	<b>Risk of Bias (low/high/unclear):</b> <u>Selection bias:</u> (low) Randomization was done via a computer-generated random-sequence and interactive voice- and Web- response system. <u>Performance bias:</u> (low) Trial was double-blind design with medication concealment using double-dummy design. <u>Detection bias:</u> (low) Outcome assessors were blinded to randomization treatment assignments. Outcomes were adjudicated by clinical-events committees. <u>Attrition bias:</u> (low) Overall attrition was 25%. mITT analysis with LOCF was used for all data. <u>Reporting bias:</u> (low) Study protocol was followed and outcomes were reported as specified.  <b>Applicability:</b> <u>Patients:</u> Patients were well matched. Ninety-nine percent of patients had a history of cardiovascular disease. <u>Intervention:</u> Pooled doses of empagliflozin 10 mg and empagliflozin 25 mg was appropriate due to the low incidence of expected events for the primary outcome. <u>Comparator:</u> Matched placebo is an appropriate comparator. <u>Outcomes:</u> composite of major cardiac events is an accepted outcome and required by the FDA to ensure antidiabetic therapy is not associated with unacceptable levels of cardiac risk. In this study, empagliflozin was shown to reduce cardiovascular outcomes including death and all-cause mortality. <u>Setting:</u> Forty-two countries and 590 outpatient centers.				
	2. Empagliflozin 25 mg (E25)								<u>PP:</u> 1. 1790 2. 1800 3. 1650	Secondary Outcomes: <b>Composite of CV death, non-fatal MI, non-fatal stroke, or hospitalization from unstable angina):</b> E*: 599 (12.8%) vs. P: 333 (14.3%); HR 0.89 (95.04% CI, 0.78 to 1.01; P<0.001 for noninferiority and p=0.08 for superiority)  <b>Hospital admission for HF:</b> E*: 126 (2.7%) vs. P: 95 (4.1%); HR 0.65 (95% CI, 0.50 to 0.85; P=0.002)  <b>CV mortality:</b> E*: 172 (3.7%) vs. P: 137 (5.9%); HR 0.62 (95% CI, 0.49 to 0.77; P<0.001)	NS	NA
	3. Placebo (P)								<u>Attrition:</u> 1. 555 (24%) 2. 542 (23%) 3. 683 (29%)			
	Study duration: 3.1 years	<u>Key Inclusion Criteria:</u> • T2DM • ≥18 years of age • Body max index of ≤45 • eGFR ≥30 ml/min/1.73m <sup>2</sup> • Established CVD • A1C 7-9% on no glucose lowering therapy or A1C of 7-10% on 12 weeks of a stable dose of glucose-lowering therapy*	<u>Key Exclusion Criteria:</u> • eGFR < 30 ml/min/1.73 m <sup>2</sup> • Liver disease • Surgery • Cancer	2.2/45	2.6/39							

		<p>* Glucose lowering treatment at baseline:</p> <ul style="list-style-type: none"> <li>- metformin (73.8%)</li> <li>- Insulin (48.0%)</li> <li>- sulfonylureas (43.0%)</li> </ul>		<p>(3.0%); HR 1.18 (95% CI, 0.89 to 1.56; P=0.26)</p> <p><b>Nonfatal stroke:</b> E*: 150 (3.2%) vs. P: 60 (2.6%); HR 1.24 (95% CI, 0.92 to 1.67; P=0.16)</p> <p><b>Fatal or nonfatal MI:</b> E*: 223 (4.8%) vs. P: 126 (5.4%); HR 0.87 (95% CI, 0.70 to 1.09; P=0.23)</p> <p>E*= Pooled data for 10 mg and 25 mg doses.</p>	NS			
<p><u>Abbreviations</u> [alphabetical order]: A1C = hemoglobin A1C; ACE = angiotensin converting enzyme; AE = adverse events; ARR = absolute risk reduction; CI = confidence interval; CV = cardiovascular; CVD = cardiovascular disease; DB = double-blind; D/C = discontinuations; eGFR = estimated glomerular filtration rate; HR = hazard ratio; MI = myocardial infarction; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = not statistically significant; PP = per protocol</p>								

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## Appendix 1: Current Status on Preferred Drug List

### Diabetes, Sodium-Glucose Co-Transporter Inhibitors

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	TABLET	FARXIGA	DAPAGLIFLOZIN PROPANEDIOL	N
ORAL	TABLET	INVOKANA	CANAGLIFLOZIN	N
ORAL	TABLET	JARDIANCE	EMPAGLIFLOZIN	N
ORAL	TAB BP 24H	XIGDUO XR	DAPAGLIFLOZIN/METFORMIN HCL	N
ORAL	TABLET	INVOKAMET	CANAGLIFLOZIN/METFORMIN HCL	N

## Appendix 2: Medline Search Strategy

Database(s): Ovid MEDLINE(R) without Revisions 1996 to October Week 4 2015

Search Strategy:

#	Searches	Results
1	sodium glucose cotransporter-2 inhibitor.mp.	58
2	limit 1 to (english language and humans and yr="2015 -Current")	5
3	dapagliflozin.mp.	174
4	canagliflozin.mp.	148
5	empagliflozin.mp.	95
6	2 or 3 or 4 or 5	359
7	limit 6 to (english language and yr="2015 -Current")	43
8	limit 7 to (clinical trial, all or clinical trial, phase iii or comparative study or controlled clinical trial or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)	23

**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 6 months

**Requires PA:**

- All SGLT-2 inhibitors

**Covered Alternatives:**

- Current PMPDP preferred drug list per OAR 410-121-0030 at [www.orpdl.org](http://www.orpdl.org)
- Searchable site for Oregon FFS Drug Class listed at [www.orpdl.org/drugs/](http://www.orpdl.org/drugs/)

Approval Criteria		
1. Is this a request for renewal of a previously approved prior authorization?	<b>Yes:</b> Go the Renewal Criteria	<b>No:</b> Go to #2
2. What diagnosis is being treated?	Record ICD10 code	
3. Does the patient have a diagnosis of type 2 diabetes mellitus?	<b>Yes:</b> Go to #4	<b>No:</b> Pass to RPh. Deny; medical appropriateness
4. Has the patient tried and failed metformin and sulfonylurea therapy, have contraindications to these treatments or is requesting a SGLT-2 inhibitor to be used with metformin and a sulfonylurea?  (document contraindication, if any)	<b>Yes:</b> Go to #5	<b>No:</b> Pass to RPh; deny and recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.

## Approval Criteria

<p>5. Is the request for the following treatments (including combination products) with an associated estimated glomerular filtration rate (eGFR):</p> <ul style="list-style-type: none"> <li>• Canagliflozin and eGFR &lt;45 mL/min/ 1.73 m<sup>2</sup>, or</li> <li>• Empagliflozin and eGFR &lt;45 mL/min/ 1.73 m<sup>2</sup>, or</li> <li>• Dapagliflozin and eGFR &lt;60 mL/min/ 1.73 m<sup>2</sup>?</li> </ul>	<p><b>Yes:</b> Pass to RPh. Deny; medical appropriateness</p>	<p><b>No:</b> Approve for up to 6 months.</p>
<p>6. Has the patient tried and failed (unable to maintain goal A1c) all of the following drugs, or have contraindications to all of these drugs?</p> <ol style="list-style-type: none"> <li>1. Insulin</li> <li>2. Thiazolidinedione</li> <li>3. DPP-4 inhibitor</li> <li>4. GLP-1 agonist</li> <li>5. Amylin analog</li> </ol>	<p><b>Yes:</b> Approve for up to 6 months.</p>	<p><b>No:</b> Pass to RPh; deny and require a trial of insulin, thiazolidinedione, DPP-4 inhibitor, GLP-1 agonist, and amylin analog.</p>

## Renewal Criteria

<p>1. Is the request for the following treatments (including combination products) with an associated estimated glomerular filtration rate (eGFR):</p> <ul style="list-style-type: none"> <li>• Canagliflozin and eGFR &lt;45 mL/min/ 1.73 m<sup>2</sup>, or</li> <li>• Empagliflozin and eGFR &lt;45 mL/min/ 1.73 m<sup>2</sup>, or</li> <li>• Dapagliflozin and eGFR &lt;60 mL/min/ 1.73 m<sup>2</sup>?</li> </ul>	<p><b>Yes:</b> Pass to RPh. Deny; medical appropriateness</p>	<p><b>No:</b> Approve for up to 6 months.</p>
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## Initiating Metformin

<p>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.</p>
<p>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).</p>
<p>3. If gastrointestinal side effects appear with increasing doses, decrease to previous lower dose and try to advance the dose at a later time.</p>
<p>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.</p>

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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*P&T/DUR Review:* 3/16 (KS); 9/15; 1/15; 9/14; 9/13  
*Implementation:* 2/15