Drug Use Research & Management Program
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New Drug Evaluation: Empagliflozin

Month/Year of Review: January 2015
Generic Name: Empagliflozin
PDL Class: Diabetes Medications

End date of literature search: October 13, 2014
Brand Name (Manufacturer): Jardiance ™ (Boehringer Ingelheim)
Dossier Received: Yes

FDA Approved Indication:[1]

Empagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor used to improve glucose control in adult patients with type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise. Empagliflozin is not for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis.

Research Questions:

- Is there evidence of superior efficacy of empagliflozin compared to other T2DM therapies when considering important outcomes such as hemoglobin A1c (HbA1c) lowering to goal and reduced microvascular and macrovascular outcomes?
- Is there evidence empagliflozin has a better safety profile than other treatments for T2DM?
- Are there subgroups that would benefit more from empagliflozin therapy or be at risk of more harm?

Conclusions:

- There is insufficient evidence at this time that empagliflozin reduces microvascular or macrovascular outcomes.
- Empagliflozin 10 mg daily and empagliflozin 25 mg daily were studied in six phase 3, randomized, fair quality clinical trials for approval.[2-7] There is moderate strength of evidence that empagliflozin is effective in reducing HbA1c in patients with T2DM. Empagliflozin 10 mg and 25 mg daily lowered HbA1c from -0.6% to -1.27% in placebo-controlled randomized trials, both as monotherapy and as adjunctive therapy.[2-7] The 25 mg dose did not offer any significant advantages over the 10 mg dose in decreasing HbA1c in these trials. Hemoglobin A1c reductions were greatest in those studies where patients had the highest mean baseline HbA1cs. Small changes in systolic blood pressure (-2 to -4 mmHg) and weight (placebo adjusted difference of about 2 kg over 24 weeks) were also found with empagliflozin therapy.[8]
- Empagliflozin was generally well tolerated. Discontinuations due to adverse effects were similar in empagliflozin groups (1-5%) and active comparators (2-4%).[2,3] Most common adverse effects are genital mycotic infections and urinary tract infections.[1]
- Empagliflozin should not be used in patients with estimated glomerular filtration rate (eGFR) ≤45 mL/min /1.73m^2 due to decreased effectiveness noted in this population.[1,8]

- Indirect comparisons demonstrate that empagliflozin lowers HbA1c the same or less than therapies on the preferred drug list (PDL). Limited long-term evidence and insufficient evidence on microvascular and macrovascular complications suggest empagliflozin use should be reserved for patients who remain hyperglycemic despite treatment with T2DM therapies on the PDL.

Recommendations:

- Recommend a prior authorization to limit use of empagliflozin to patients that have tried and failed other treatments for T2DM (Appendix 1). No changes to the PDL are recommended.

Reason for Review:

Empagliflozin is a SGLT-2 inhibitor used for the treatment of T2DM. Comparison of efficacy and safety data of empagliflozin to other T2DM treatments is necessary for the management of the PDL and prior authorization (PA) criteria.

Background:

Type 2 diabetes mellitus is a prevalent disease which affects an estimated 25.6 million people in the United States.[9] Despite a variety of treatments a significant number of patients fail to meet A1C goals and within three years of being diagnosed 50% of patients require combination therapy to control rising glucose levels. According to the Centers for Disease Control and Prevention (CDC), as many as 1 in every 3 adults will have T2DM by 2050.[10] Treatment guidelines recommend a trial of lifestyle modifications to control hyperglycemia in patients with T2DM and add pharmacotherapy for persistent elevated glucose levels. Guidelines recommend a goal HbA1C of less than 7% to minimize macrovascular and microvascular complications. Lower or higher HbA1c goals may be appropriate depending on patient specific characteristics. Therapy should be tailored according to patient factors, such as concomitant comorbidities.[11,12] A number of therapeutic options are available for management of glycemic variances associated with T2DM.[13] Classes of anti-hyperglycemic agents (AHA) currently available are: alpha-glucosidase inhibitors, biguanides, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogues, SGLT2 inhibitors, insulins, meglitinides, sulfonylureas, thiazolidinediones (TZD), bile acid sequestrants, dopamine-2 agonists and amylin mimetics.

Important outcomes in patients with diabetes are: mortality, microvascular complications (chronic kidney disease, retinopathy, peripheral neuropathy) and macrovascular complications (cardiovascular events, stroke/ischemic attacks, coronary heart disease, amputations). Intermediate outcomes of interest are HbA1C and weight. Adverse event outcomes are: severe adverse events, hypoglycemia rates, and withdrawals due to adverse events. Hemoglobin A1C is often used as a surrogate outcome to assess comparative efficacy of different AHA therapies, as hyperglycemia has been shown to correlate with microvascular complications and potentially macrovascular outcomes.[12] Available data are limited to short-term studies, which prevents the assessment of the durability of available AHAs to control glucose levels long-term and to compare the effectiveness of AHAs on outcomes such as microvascular and macrovascular complications. Differing definitions of hypoglycemia also complicate the comparisons of safety between the differing AHA agents. Available evidence suggests that metformin is likely to reduce the incidence of cardiovascular disease based on data from the United Kingdom Prospective Diabetes Study (UKPDS) trial.[12] UKPDS data has also indicated a reduced incidence of microvascular risk with sulfonylureas and insulin therapy. Thiazolidinediones, alpha-glucosidase inhibitors and dopamine-2 agonists have studies that suggest reduced cardiovascular disease events but additional data are needed.[12] The effects of many of the AHAs on long-term complications of T2DM remain unknown.

Clinical Efficacy:

Empagliflozin was studied in six, phase three, fair-quality studies.[2-7] Studies evaluated daily empagliflozin 10 mg and empagliflozin 25 mg. Three studies included an empagliflozin 25 mg open-label treatment arm.[2,5,7] Five were placebo-controlled (one with sitagliptin as a reference agent)[2,4-7] and one was a non-inferiority study with glimepiride.[3] One study evaluated empagliflozin as monotherapy and five studies were studies as adjunctive therapy for the following treatments: metformin, sulfonylureas, pioglitazone and insulin. Patients were a mean age of 56 years and mean HbA1cs between 7.88% and 8.34%. The primary endpoint was change in baseline HbA1c for all studies. Secondary endpoints of interest were changes in weight and blood pressure.

Roden, et al.[2]
In this fair quality trial of patients not previously on treatment for T2DM, patients were randomized to empagliflozin 10 mg daily, empagliflozin 25 mg daily, sitagliptin 100 mg daily or placebo. At 24 weeks, reductions in HbA1c were similar between the three treatment groups. Reductions in HbA1c for empagliflozin 10 mg, empagliflozin 25 mg, sitagliptin, placebo and open-label empagliflozin 25 mg were -0.66%, -78%, -0.66%, 0.08% and -3.70%, respectively. Mean systolic blood pressure reductions were significantly greater for empagliflozin 10 mg and 25 mg compared to placebo and sitagliptin. Reductions in body weight from baseline were significantly lower in the empagliflozin groups compared to sitagliptin and placebo. Exploratory analysis found less hyperglycemia rescue was needed in the active treatment group compared to placebo.

Ridderstrale, et al.[3]
In this fair quality trial, empagliflozin 25 mg daily was compared to glimepiride 1-4 mg daily (mean 2.71 mg) in 1545 patients with T2DM and concomitant metformin therapy. Patients were a mean age of 55 years old with a mean baseline HbA1c of 7.92%. Patients had normal renal function and a high percentage were on cardiovascular medications (76%) and had uncontrolled blood pressure (69%). Empagliflozin was non-inferior to glimepiride at 52 weeks, with HbA1c lowering of -0.73% and -0.66%, respectively. At 104 weeks, patients on empagliflozin had a lower HbA1c compared to patients on glimepiride (treatment difference -0.11 (95% CI -0.19 to -0.02, p<0.0001 for non-inferiority and p=0.0153 for superiority). Exploratory analysis found significantly less hyperglycemia rescue treatment was needed in the empagliflozin treatment group compared to glimepiride and a similar amount of patients in each group obtained a HbA1c of less than 7%. Mean dose of glimepiride was low and only 40% reached the maximum allowed dose of 4 mg daily.

Kovacs, et al.[4]
In a 24-week trial, 498 patients were treated with empagliflozin 10 mg daily, empagliflozin 25 mg daily or placebo with concomitant pioglitazone with or without metformin. Patients were a mean age of 55 years with a baseline HbA1c of 8.1%. A majority (76%) of enrolled patients were on pioglitazone and metformin. A smaller percentage (24%) were on pioglitazone alone. Empagliflozin was superior to placebo for both doses. Hemoglobin A1c reductions were the following: -0.6% for empagliflozin 10 mg, -0.7% for empagliflozin 25 mg and -0.1% for placebo (p<0.001 for both comparisons). Efficacy of empagliflozin was consistent regardless if patients were on pioglitazone or pioglitazone plus metformin.

Häring, et al.[5]
A fair quality study compared daily empagliflozin 10 mg and empagliflozin 25 mg to placebo in a 24-week study of patients with T2DM taking metformin and a sulfonylurea. Patients were a mean age of 56 years, had a mean baseline HbA1c of 8.1% and were well matched. Empagliflozin 10 mg was superior to placebo with a treatment difference of -0.64% [95% CI -0.77 to -0.51]. Empagliflozin 25 mg was also superior to placebo with a treatment difference of -0.59% (95% CI -

0.73 to -0.46). Both doses of empagliflozin were found to be superior to placebo for reductions in body weight and mean daily glucose at 24 weeks. In an exploratory analysis, more patients in both empagliflozin groups obtained an HbA1c less than 7% compared to placebo.

Rosenstock, et al.[6]
In a 52-week study, daily empagliflozin 10 mg and 25 mg in combination with insulin were compared to placebo plus insulin. Over 500 hundred obese patients with history of previous insulin with or without metformin use were included. Insulin doses were to remain stable up to week 18. During weeks 19-40, insulin doses were adjusted to meet a preprandial glucose target of less than 100 mg/dL and postprandial glucose less than 140 mg/dL. During weeks 41-52, insulin doses were kept stable according to changes made during adjustment period. Included patients were a mean age of 57 years, had a baseline HbA1c of 8.34%, mean BMI of 34.8 kg/m2 and mean insulin dose of 92 units. At week 18, empagliflozin 10 mg was superior to placebo for HbA1c lowering (treatment difference -0.44% [95% CI -0.59 to -0.29, p<0.001]). Empagliflozin 25 mg was superior to placebo (treatment difference -0.52% [95% CI -0.67 to -0.37, p<0.001]). Both groups of empagliflozin-treated patients had greater HbA1c reduction compared to placebo. and weight loss in the empagliflozin groups was superior to placebo. Hypoglycemia rates were similar between groups and much higher than in other studies, most likely a consequence of background insulin use.

Häring, et al.[7]
In a fair quality study, patients on metformin were randomized to daily empagliflozin 10 mg, empagliflozin 25 mg or placebo. Included patients were considered overweight (mean BMI 29.2 kg/m^2), with moderately uncontrolled T2DM (mean HbA1c 7.9%), mean age of 56 years and normal renal function. Patients with an HbA1c of 10% or higher were candidates for treatment in the open-label treatment arm with empagliflozin 25 mg daily. At 24 weeks, empagliflozin 10 mg daily was superior to placebo, decreasing HbA1c by -0.70% vs. -0.13%, respectively. Empagliflozin 25 mg was also superior to placebo and decreased HbA1c by 0.77% from baseline. HbA1c lowering in the open-label empagliflozin 25 mg group was -3.23%.

Limitations of these studies are related to study design. There is a potential for performance and detection bias due to lack of details on blinding and assessment. Most studies allowed for titration of antihypertensive treatments, which may influence diastolic and systolic blood pressure outcomes noted in some trials. As with other SGLT2 inhibitors, efficacy of empagliflozin decreases as renal function declines. FDA subgroup analyses found those younger than 50 years of age responded better to empagliflozin 25 mg (HbA1c change -0.86%) compared to those older than 75 years (HbA1c change -0.54%). Hemoglobin A1c of men also respond better to empagliflozin 25 mg daily than women (men -0.76%, women -0.58%). These differences may be due to a decline in eGFR, which reduces the effectiveness of empagliflozin.

<u>Clinical Safety:</u>
Most common adverse reactions occurring in greater than 5% of patients with empagliflozin were urinary tract infections and female genital mycotic infections.[1] Most genital and urinary tract infections were mild and unrelated to dose.[1,8] Risk of hypoglycemia was similar between empagliflozin and placebo treated patients, 19.9% and 21.9%, respectively.[8] Volume depletion and associated hypotension in patients at increased risk (elderly, renal impairment, low systolic blood pressure and diuretic use) were more common with empagliflozin versus comparators. Increases in HDL cholesterol levels were noted with empagliflozin with no changes in other lipid parameters. Small increases in hematocrit and reductions in uric acid levels were also noted. Elevated liver enzymes with associated increases in bilirubin have been seen in studies but no clear cause and effect relationship associated with empagliflozin has been determined.[1] In an ongoing cardiovascular outcomes trial, hepatic events are also being evaluated.[8]

Conclusion:
There is moderate strength of evidence that empagliflozin lowers HbA1c levels ranging from -0.6% to -1.18%, as demonstrated in randomized placebo-controlled trials, both as monotherapy and as adjunct therapy. Small decreases in weight and low incidences of hypoglycemia are also noted with this treatment. Common adverse events include urinary tract and genital mycotic infections.

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:
1) Microvascular outcomes
2) Macrovascular outcomes
3) Goal HbA1c
4) Hypoglycemia
5) Quality of life
6) Serious adverse reactions
7) Changes in weight

Primary Study Endpoint:
1) Change in HbA1c from baseline

Ref./Study Design	Drug Regimens/ Duration	Patient Population	N mITT (per-protocol)	Outcomes/ Efficacy Results (98.5% CI, p-values	ARR/ NNT	Safety Results (CI, p-values)	ARR/ NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns
Roden, et al 2013[2] DB, PC, Phase 3, RCT 124 Centers and 9 Countries	1. Empagliflozin 10 mg PO daily (E10) 2. Empagliflozin 25 mg PO daily (E25) 3. Sitagliptin 100 mg PO daily (S) (reference agent) 4. Placebo PO daily (P) 5. Open-label Empagliflozin 25 mg PO daily in patients with HbA1c >10% (OLE) - Patients received 2-week open label placebo run-in, except for those	**Demographics (for randomized patients):** Age (mean): 55 years Female: 40% Baseline HbA1c (mean): 7.88% BMI (mean): 28.4 kg/m^2 **Inclusion Criteria:** Patients ≥18 years old, body mass index of ≤45 kg/m^2, non-pregnant and non-lactating, HbA1c of 7-10% (7-9% in Germany) or >10% if enrolled in open label arm, with T2DM and not on any treatment for T2DM for at least 12 months before randomization or start of	1. 224 (206) Attrition: 8% 2. 224 (204) Attrition: 9% 3. 223 (206) Attrition: 8% 4. 228 (187) Attrition: 18% 5. 87 (78)	**Primary Outcome** **Change in HbA1c at 24 weeks:** E10: -0.66% E25: -0.78% S: -0.66% P: 0.08% OLE: -3.70% E10 vs P: -0.74 (95% CI -0.88 to -0.59, p<0.001) E25 vs P: -0.85 (95% CI -0.99 to -0.71,p<0.001) E10 vs S: 0.00 (95% CI -0.15 to 0.14,	N/A	**Discontinuations due to Adverse Events:** E10: 2 (1%) E25: 4 (2%) S: 5 (2%) P: 8 (3%) OLE: 3 (3%) p-value not reported **Hypoglycemia:** E10: 1 (<1%) E25: 1 (<1%) S: 1 (<1%) P: 1 (<1%) OLE: 0 p-value not reported **Urinary tract**		**Quality rating:** Fair **Internal Validity:** Selection: Randomized via a computer generated random sequence. Performance: Patients and caregivers blinded. No details provided. Detection: Assessors blinded. No details were provided Attrition: Low overall attrition; mITT analysis with LOCF. **External Validity:** Recruitment: Patients from 124 centers and 9 countries were included. Open label arm was not conducted in Germany or Ireland. Patient Characteristics: Patients with mildly elevated HbA1c (mean baseline HbA1c 7.88%) and normal renal function. Patients had no prior treatment for T2DM. Outcomes: Accepted surrogate end-point used. Data on long-term health outcomes are lacking.

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	randomized to open-label treatment arm. * Trial was 24 weeks	open-label treatment phase. **Exclusion Criteria:** eGFR of <50 mL/min /1.73m^2 or <60 mL/min /1.73m^2 in China, contraindications to sitagliptin, treatment of anti-obesity drugs within previous 3 months, systemic corticosteroids, uncontrolled thyroid disease, or endocrine disorder outside of T2DM.	Attrition: 10%	p=0.9697) E25 vs S: -0.12 (95% CI -0.26 to 0.03, p=0.1060) **<u>Secondary Outcomes</u>** **Change in weight at 24 weeks (kg):** E10: -2.26 E25: -2.48 S: 0.18 P: -0.33 OLE: -2.43 E10 vs.P: P<0.0001 E25 vs. P: P<0.0001 S vs. P: P<0.0001 E10 vs. S: P<0.0001	N/A	**infection:** E10: 15 (7%) E25: 12 (5%) S: 11 (5%) P: 12 (5%) OLE: 3 (3%) p-value not reported **Genital infections:** E10: 7 (3%) E25: 9 (4%) S: 2 (1%) P: 0 OLE: 1 (1%) p-value not reported		**Analysis:** In patients with mildly uncontrolled T2DM, empagliflozin 10 mg and 25 mg significantly reduced HbA1c by 0.74 and 0.86%, respectively. Patients on empagliflozin, a mild diuretic, also lost about 2 kg of body weight and systolic blood pressure decreased 2.6 and 3.4 mmHg versus placebo with 10 mg and 25 mg, respectively. Empagliflozin use resulted in increased genital mycotic infections.
Ridderstråle, et al 2013[3] DB, PC, Phase 3, RCT 173 Centers and 23 Countries	1. Empagliflozin 25 mg PO daily (E) 2. Glimepiride 1-4 mg PO daily (G) • Patients were on background metformin • Patients had an open-label run-in/stabilization period of 2 weeks • Treatment	**Demographics:** Age (mean): 55 years Male: 54% Baseline HbA1c (mean): 7.92% BMI (mean): 30 kg/m^2 **Inclusion Criteria:** Patients with T2DM, ≥18 years old, body mass index of ≤45 kg/m^2, HbA1c of 7-10% with T2DM and experiencing inadequate glycemic control while taking	1.765 (648 Attrition: 15% 2.780 (648 Attrition: 17%	**<u>Primary Outcome</u>** **Change in HbA1c at 52 weeks:** E: -0.73% G: -0.66% Treatment difference: -0.07 (95% CI -0.15 to 0.01, p<0.0001 for non-inferiority) **<u>Secondary Outcomes</u>**	N/A	**Discontinuations due to Adverse Events:** E: 39 (5%) G: 34 (4%) **Hypoglycemia at week 52:** E: 12 (2%) G: 159 (20%) P<0.0001 **Hypoglycemia at week 104:** E: 19 (2%)		**Quality rating:** Fair **Internal Validity:** <u>Selection:</u> Computer generated random sequence. <u>Performance:</u> Patients and caregivers blinded and efforts were made to conceal treatment allocation. <u>Detection:</u> No details were provided. <u>Attrition:</u> Moderate attrition; ITT analysis with LOCF. **External Validity:** <u>Recruitment:</u> Patients from 173 centers and 23 countries were included. <u>Patient Characteristics:</u> Majority (69%) of patients had uncontrolled blood pressure at time of study entry. Thirteen percent of

	duration 104 weeks • 2 year extension	background metformin for ≥12 weeks before screening. **Exclusion Criteria:** eGFR ≤60 mL/min/1.73m^2, avg blood glucose >240 mg/dL (HbA1c >10%) after overnight fast, use of other antidiabetic drugs other than metformin within 12 weeks of randomization.		**Change in HbA1c at 104 weeks:** E: -0.66% G: -0.55% Treatment difference: -0.11 (95% CI -0.19 to -0.02, p<0.0001 for non-inferiority and p=0.0153 for superiority) **Change in weight at week 104:** E: -3.2 kg G: 1.3 kg Treatment difference: -4.61 (95% CI, 4.8 to -4.1, p<0.0001)	N/A N/A	G: 189 (24%) P<0.0001 **Urinary tract infection:** E: 95 (12%) G: 99 (13%) p-value not reported **Genital infections:** E: 90 (12%) G: 17 (2%) p-value not reported		participants were from North America. The mean dose of glimepiride was 2.71 mg/day. Outcomes: Accepted surrogate end-point used. Data on long-term health outcomes are lacking. **Analysis:** Study showed durability of empagliflozin efficacy out to 104 weeks. Lack of titration of glyburide dose beyond mean dose of 2.71 mg/day may have influenced results.
Kovac, et al 2013[4] (EMPA-REG PIO) DB, PG, RCT 69 Centers in 8 countries	1. Empagliflozin 10 mg PO daily (E10) 2. Empagliflozin 25 mg PO daily (E25) 3. Placebo PO daily (P) • Patients on pioglitazone ± metformin. • Study duration was 24 weeks • 2 weeks of placebo run-in	**Demographics:** Age (mean): 55 years Male: 48% Baseline HbA1c (mean): 8.1% BMI (mean): 29 kg/m^2 **Inclusion Criteria:** Patients with T2DM ≥18 years old (and ≤65 years in India), body mass index of ≤45 kg/m^2, HbA1c of 7-10%, on a diet and exercise program with an unchanged dose of pioglitazone monotherapy or pioglitazone plus metformin for ≥12 weeks before randomization. **Exclusion Criteria:**	1. 165 (154) Attrition: 7% 2.168 (156) Attrition: 7% 3.165 (147) Attrition: 11%	**<u>Primary Outcome</u>** **Change in HbA1c from baseline at 24 weeks:** E10: -0.6% E25: -0.7% P: -0.1% P<0.001 for both group comparisons **<u>Secondary Outcomes</u>** **Change in weight at week 24:** E10: -1.62 kg E25: -1.47 kg P: 0.34 kg E10 vs. P: P<0.001 E25 vs. P: P<0.001	N/A N/A	**Discontinuations due to Adverse Events:** E10: 2 (1.2%) E25: 5 (3.0%) P: 4 (2.4%) p-value not given **Hypoglycemia:** E10: 2 (1.2%) E25: 4 (2.4%) P: 3 (1.8%) p-value not given **Urinary Tract Infection:** E10: 24 (14.5%) E25: 18 (10.7%) P: 18 (10.9%) p-value not given ***Genital Infections:**		**Quality rating:** Fair **Internal Validity:** <u>Selection:</u> Patients were randomized via a computer-generated randomization sequence with a voice response system. <u>Performance:</u> Patients and caregivers blinded; no details provided. <u>Detection:</u> No details provided. <u>Attrition:</u> Attrition was low in all groups (7-11%), mITT analysis with LOCF **External Validity:** <u>Recruitment:</u> Patients from 69 centers and 8 countries included. <u>Patient Characteristics:</u> Seventy-six percent of patients on pioglitazone and metformin while 25% only taking pioglitazone. <u>Outcomes:</u> Accepted surrogate end-point used. Data on long-term health outcomes are lacking. **Analysis:** Study of short duration demonstrated that

		Uncontrolled T2DM (avg glucose >240 mg/dL or HbA1c >10%), severe renal impairment, liver disease, contraindication to pioglitazone or metformin, cardiovascular or cerebrovascular disease within 3 months, on anti-obesity medication within 3 months, bariatric surgery within previous 2 years, systemic corticosteroid use, change in thyroid dose in previous 6 weeks, or endocrine disorder besides T2DM.				E10: 14 (8.5%) E25: 6 (3.6%) P: 4 (2.4%) p-value not given * Events consistent with infection		empagliflozin was superior to placebo in patients on background pioglitazone ± metformin.
Häring, et al 2013[5] (EMPA-REG METSU) DB, PC, Phase 3, RCT 148 Centers in 12 countries	1. Empagliflozin 10 mg PO daily (E10) 2. Empagliflozin 25 mg PO daily (E25) 3. Placebo PO daily 4. Open-label empagliflozin 25 mg PO daily (OLE) • Patients from both groups on background metformin (≥1500 mg/day) and a sulfonylurea (≥ to half the maximum recommended dose or maximum tolerated dose or maximum dose according to the label).	**Demographics (for randomized patients):** Age (mean): 57 years Male: 51% Baseline HbA1c (mean): 8.10% BMI (mean): 28.2 kg/m^2 **Inclusion Criteria:** Patients ≥18 years with T2DM inadequately controlled on metformin and a sulfonylurea for ≥12 weeks and <5 years; HbA1c ≥7.0% to ≤ 10% and BMI ≤45kg/m^2. Patients with a HbA1c ≥10% were candidates for treatment in the open-label treatment arm. **Exclusion Criteria:** Patients with uncontrolled hyperglycemia (avg glucose ≥240 mg/dL or HbA1c ≥10%), acute cardiovascular or cerebrovascular incident	1. 225 (208) Attrition: 8% 2. 216 (199) Attrition: 8% 3. 225 (201) Attrition: 11% 4. 101 (85) Attrition: 16%	**<u>Primary Outcome</u>** **Change in HbA1c from baseline at 24 weeks:** E10: -0.82% E25: -0.77% P: -0.17% OLE: -2.89% Treatment difference E10 vs. P: -0.64% (95% CI -0.77 to -0.51, p<0.001) Treatment difference for E25 vs. P: -0.59% (95% CI -0.73 to -0.46, p<0.001) **<u>Secondary Outcomes</u>** **Change in weight at 24 weeks:**	NA N/A	**Discontinuations due to Adverse Events:** E10: 6 (2.7%) E25: 7 (3.2%) P: 8 (3.6%) OLE: 5 (5%) p-value not reported **Hypoglycemia:** E10: 36 (16.1%) E25: 25 (11.5%) P: 19 (8.4%) OLE: 7 (6.9%) p-value not reported **Urinary tract infections:** E10: 10.3% E25: 8.3% P: 8% OLE: 3 (3%) p-value not reported **Genital infections:**		**Quality rating:** Fair **Internal Validity:** <u>Selection:</u> Use of third-party interactive voice and web response system. <u>Performance:</u> No details on blinding were provided. <u>Detection:</u> No details were provided. <u>Attrition:</u> Low overall attrition (9% discontinued); mITT analysis done, with LOCF for missing data. **External Validity:** <u>Recruitment:</u> Patients were recruited from 148 centers in 12 countries. <u>Patient Characteristics:</u> A majority of patients (77%) were diagnosed with T2DM for >5 years. Less patients in the empagliflozin 10 mg group (2.2%) and empagliflozin 25 mg group (0.9%) required rescue therapy compared to placebo (12%). <u>Outcomes:</u> Accepted surrogate end-point used. Data on long-term health outcomes are lacking.

	• Open-label placebo run-in for 2 weeks for randomized groups. • Treatment duration was 24 weeks.	within 3 months or randomization, liver disease, renal disease (<30 mL/min/1.73 m2), contraindications to metformin or sulfonylureas, GI surgeries, cancer, blood dyscrasias, treatment with anti-obesit drugs, systemic steroid use change in thyroid dose within 6 weeks of study or drug or alcohol abuse.		E10: -0.97 kg E25: -1.54 kg P: -0.34 kg P<0.001 for both comparisons		E10: 6 (2.7%) E25: 5 (2.3%) P: 2 (0.9%) OLE: 2 (2%) p-value not reported		
Rosenstock, et al 2014[6] (EMPA-REG) DB, PC, PG, Phase 3, RCT 104 Centers in 14 countries	1. Empagliflozin 10 mg PO daily (E10) 2. Empagliflozin 25 mg PO daily (E25) 3. Placebo PO daily • Multi-daily injections of insulin ± metformin as background treatment. • First 18 weeks insulin dose was kept stable. • Weeks 19-40 insulin doses were adjusted to achieve glucose targets. • Weeks 41-52 insulin dose was kept stable. • Open-label placebo run-in for 2 weeks. • Treatment duration was 52 weeks.	**Demographics:** Age (mean): 57 years Male: 45% Baseline HbA1c (mean): 8.34% BMI (mean): 34.8 kg/m^2 Insulin dose (mean): 92 units daily **Inclusion Criteria:** Patients ≥18 years with T2DM, HbA1c ≥7.5% to ≤ 10% and BMI ≥30 to ≤45kg/m^2, insulin dose >60 units daily ± metformin, with changes in insulin dose >10% and no change in metformin dose within 12 weeks of study. **Exclusion Criteria:** Patients with uncontrolled hyperglycemia (avg glucose ≥240 mg/dL or HbA1c ≥10%), acute cardiovascular or cerebrovascular within 3 months or randomization, liver disease, renal disease (<60 mL/min/1.73 m2), contraindications to metformin or	1. 186 (155) Attrition: 17% 2. 189 (163) Attrition: 14% 3. 188 (157) Attrition: 16%	**<u>Primary Outcome</u>** **Change in HbA1c from baseline at 18 weeks:** E10: -0.94% E25: -1.02% P: -0.50% Treatment difference E10 vs. P: -0.44% (95% CI -0.59 to -0.29, p<0.001) Treatment difference for E25 vs. P: -0.52% (95% CI -0.67 to -0.37, p<0.001) **<u>Secondary Outcomes</u>** **Change in HbA1c from baseline at 52 weeks:** E10: -1.18% E25: -1.27% P: -0.81%	N/A N/A	**Discontinuations due to Adverse Events:** E10: 10 (5%) E25: 9 (5%) P: 9 (5%) p-value not reported **Hypoglycemia:** E10: 97 (52%) E25: 110 (58%) P: 111 (59%) p-value not reported **Urinary tract infections:** E10: 29 (16%) E25: 29 (15%) P: 29 (15%) p-value not reported **Genital infections:** E10: 8 (4%) E25: 18 (10%) P: 3 (2%) p-value not reported		**Quality rating:** Fair **Internal Validity:** <u>Selection:</u> Use of third-party interactive voice and web response system. <u>Performance:</u> No details on blinding were provided. <u>Detection:</u> No details were provided. <u>Attrition:</u> Overall attrition was 16%; mITT analysis done with LOCF for missing data. **External Validity:** <u>Recruitment:</u> Patients were recruited from 104 centers in 14 countries. <u>Patient Characteristics:</u> Patients were considered obese on high daily doses of insulin. Insulin dose changes from baseline were significantly less in both empagliflozin groups compared to placebo. <u>Outcomes:</u> Accepted surrogate end-point used. Data on long-term health outcomes are lacking.

		sulfonylureas, GI surgeries, cancer, blood dyscrasias, treatment with anti-obesit drugs, systemic steroid use change in thyroid dose within 6 weeks of study or drug or alcohol abuse, or use of investigational drug within 30 days.		Treatment difference E10 vs. P: -0.38% (95% CI -0.59 to -0.16, p<0.001) Treatment difference for E25 vs. P: -0.46% (95% CI -0.67 to -0.25, p<0.001) **Change in weight at week 52:** E10: -1.95 kg E25: -2.04 kg P: 0.44 kg P<0.001 for both comparisons	N/A			
Häring, et al 2014[7] (EMPA-REG MET) DB, PC, Phase 3, RCT 148 Centers in 12 countries	1. Empagliflozin 10 mg PO daily (E10) 2. Empagliflozin 25 mg PO daily (E25) 3. Placebo PO daily 4. Open-label empagliflozin 25 mg PO daily (OLE) • Both groups on background metformin (>1500 mg/day) • Open-label placebo run-in for 2 weeks for randomized groups. • Treatment duration was 24 weeks.	**Demographics (for randomized patients):** Age (mean): 56 years Male: 57% Baseline HbA1c (mean): 7.9% BMI (mean): 29.2 kg/m^2 **Inclusion Criteria:** Patients ≥18 years with T2DM inadequately controlled on metformin and for ≥12 weeks; HbA1c ≥7.0% to ≤ 10% and BMI ≤45kg/m^2. Patients with HbA1c ≥10% were candidates for treatment i the open-label treatment arm. **Exclusion Criteria:** Patients with uncontrolled hyperglycemia (≥240 mg/dL), acute	1. 217 (209) Attrition: 4% 2. 213 (196) Attrition: 8% 3. 207 (186) Attrition: 10% 4. 69 (58) Attrition: 16%	**<u>Primary Outcome</u>** **Change in HbA1c from baseline at 24 weeks:** E10: -0.70% E25: -0.77% P: -0.13% OLE: -3.23% Treatment difference E10 vs. P: -0.57% (95% CI -0.70 to -0.43, p<0.001) Treatment difference for E25 vs. P: -0.64% (95% CI -0.77 to -0.50, p<0.001)	N/A	**Discontinuations due to Adverse Events:** E10: 2 (0.9%) E25: 5 (2.3%) P: 7 (3.4%) OLE: 1 (1.4%) p-value not given **Hypoglycemia:** E10: 4 (1.8%) E25: 3 (1.4%) P: 1 (0.5%) OLE: 2 (2.9%) p-value not given **Urinary tract infections:** E10: 11 (5.1%) E25: 12 (5.6%) P: 10 (4.9%) OLE: 5 (7.2%) p-value not given		**Quality rating:** Fair **Internal Validity:** <u>Selection:</u> Use of third-party interactive voice and web response system. <u>Performance:</u> No details on blinding were provided. <u>Detection:</u> No details were provided. <u>Attrition:</u> Low overall attrition (7% discontinued); mITT analysis done, with LOCF for missing data. **External Validity:** <u>Recruitment:</u> Patients were recruited from 148 centers in 12 countries. <u>Patient Characteristics:</u> Patients were overweight with moderately uncontrolled T2DM and normal renal function. <u>Outcomes:</u> Accepted surrogate end-point used. Data o long-term health outcomes are lacking.

		cardiovascular or cerebrovascular incident within 3 months or randomization, liver disease, renal disease (<30 mL/min/1.73 m2), contraindications to metformin, GI surgeries, cancer, blood dyscrasias, treatment with anti-obesit drugs, use of treatment that causes unstable body weight, systemic steroid use, change in thyroid dose within 6 weeks of study or drug or alcohol abuse.		**Secondary Outcomes** **Change in weight at 24 weeks:** E10: -2.08 kg E25: -2.46 kg P: -0.45 kg P<0.001 for both above comparisons OLE: -1.91 kg	N/A	**Genital infections:** E10: 8 (3.7%) E25: 10 (4.7%) P: 0 (0%) OLE: 1 (1.4%) p-value not given		
Key: AEs: adverse events, BMI: body mass index, DB: double-blind, DBP: diastolic blood pressure, D/C: discontinuation, eGFR: estimated glomerular filtration rate, GI: gastrointestinal, HbA1c: hemoglobin A1c, kg: kilogram, LOCF: last observation carried forward, MC: multicenter, mITT: modified intent to treat, NA: not applicable, PC: placebo-controlled, PG: parallel group, RCT: randomized controlled trial, SBP: systolic blood pressure, T2DM: type 2 diabetes mellitus								

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Appendix 1: Proposed/Current PA Criteria

Sodium-Glucose Co-Transporter 2 (SGLT2)

Initiative:

- Optimize appropriate prescribing of SGLT2s.

Length of Authorization:

Up to 12 months

Requires PA:

- Non-preferred drugs

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. Does the patient have a diagnosis of Type 2 diabetes?	Yes: Go to #2	No: Deny based on appropriateness of therapy.
2. Has the patient tried and failed metformin and sulfonylurea therapy or have contraindications to these treatments? Contraindications include: • Renal disease or renal dysfunction • Known hypersensitivity to therapies • Acute or chronic metabolic acidosis • Patients at increased risk of lactic acidosis (CHF, advanced age, impaired hepatic function) • Increased risk of hypoglycemia	Yes: Go to #3	No: Recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.

Author: Kathy Sentena, Pharm.D.

Approval Criteria		
3. Is the patient requesting the following treatments (including combination products) with an associated estimated glomerular filtration rate (eGFR): • canagliflozin and eGFR <45 mL/min/1.73 m^2 or • empagliflozin and eGFR <45 mL/min/1.73 m^2 or • dapagliflozin and eGFR <60 mL/min/1.73 m^2	Yes: Deny based on appropriateness of therapy.	No: Go to #4.
4. Has the patient tried and failed third-line* treatments for type 2 diabetes or have contraindications to third-line* treatments? *Insulins, thiazolidinediones, incretin enhancers (DPP-4 inhibitors), incretin mimetics (GLP-1 agonists) or amylin analogs	Yes: Approve for up to 12 months.	No: Deny. Require a trial of third-line agents.

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 31;1-11, 2008.

P&T / DUR Action: 1/15 (KS), 9/14 (KS), 9/13 (KS)
Revision(s): 1/15
Initiated: 9/13

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Appendix 2: Specific Drug Information

CLINICAL PHARMACOLOGY [1]

Empagliflozin works by inhibiting SGLT2, which is responsible for reabsorption of glucose from the glomerular filtrate back into circulation. This in turn results in reduced renal reabsorption of filtered glucose and lowers the renal threshold for glucose and increases urinary glucose excretion.

PHARMACOKINETICS[1]

Parameter	Result
Oral Bioavailability	Not provided
Protein Binding	86%
Elimination	Feces/urine
Half-Life	12.4 hours
Metabolism	Glucuronidation

DOSE & AVAILABILITY[1]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
10 mg and 25 mg	Oral	Once daily	Once daily	Renal function should be assessed before starting and periodically during treatment. Do not initiate in patients with an eGFR <45 mL/min/1.73 m^2. No dose adjustment if eGFR is >45 mL/min/1.73 m^2.	None given	Not studied	No dose adjustments needed based on age. Monitor renal function.	• May give without regard to meals or time of day

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DRUG SAFETY [1]

Serious (REMS, Black Box Warnings, Contraindications):

- Black Box: No black box warnings for empagliflozin.
- REMS: REMS not required for empagliflozin.
- Contraindications: Do not use empagliflozin in patients with severe renal impairment , end-stage renal disease, dialysis or hypersensitivity to empagliflozin.

Warnings and Precautions:

- Empagliflozin causes intravascular volume contraction. Hypotension may occur with treatment. Those who are elderly, have renal impairment, low systolic blood pressure, and those on diuretics may be at increased risk. Monitor volume status before initiating therapy and correct if needed. Monitor for signs and symptoms of hypotension throughout treatment.
- Monitor renal function during empagliflozin therapy. Monitor more often in patients with eGFR <60 mL/min/1.73 m^2.
- Hypoglycemia may occur more often in patients on insulin secretagogues or insulin, consider reducing the dose when initiating empagliflozin.
- Empagliflozin has been associated with an increased risk of genital mycotic infections, urinary tract infections and increased LDL-C. Treat if needed.

Monitoring: Monitor renal function in patients with renal impairment.

Drug-Drug interactions: If diuretics are used with empagliflozin there may be an increased risk of volume depletion. Use of empagliflozin with insulin or insulin secretagogues increases the risk of hypoglycemia.

Food-Drug Interactions: No food-drug interactions have been identified.

Pregnancy/lactation rating: Category C. Empagliflozin has not been adequately studied in pregnant women. Data are insufficient to recommend empagliflozin in women who are lactating.

ADVERSE REACTIONS[1]

Adverse reactions occurring in ≥5% of patients treated with empagliflozin were urinary tract infections and female genital mycotic infections.

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