

Empagliflozin (Jardiance) National Drug Monograph

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

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information

Description/Mechanism of Action

The kidney plays a major role in glucose homeostasis through glomerular filtration and reabsorption of glucose. Renal reabsorption of glucose is mediated by sodium-glucose co-transporter (SGLT) 1 and SGLT2 within the proximal tubule. SGLT2 is expressed almost exclusively in the kidney and is responsible for the majority of glucose reabsorption. SGLT1 is primarily expressed along the brush border of the small intestine and is also located in the proximal tubule; it is mainly responsible for glucose absorption in the GI tract, but also accounts for approximately 10% of glucose reabsorption at the proximal renal tubule. Inhibiting SGLT2 decreases plasma glucose by increasing urinary glucose excretion.

Indication(s) Under Review

As an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes

Dosage Form(s) Under Review

10 and 25mg tablets

REMS

REMS No REMS

See Other Considerations for additional REMS information

Pregnancy Rating

Category C

Executive Summary	
Efficacy	<ul style="list-style-type: none"> Reduction in A1C generally <1% 11-29% of patients treated with empagliflozin had ≥5% weight loss from baseline (magnitude of change was less when combined with drugs known to cause weight gain such as SU, TZDs, insulin)
Safety	<ul style="list-style-type: none"> Similar to the other agents in the SGLT2 inhibitor class, there is an increased risk in genital mycotic infections, urinary tract infections, hypotension, and small increases in serum creatinine and decreases in eGFR Low risk for hypoglycemia Can reduce systolic blood pressure (means ranged from 2.9 to 5.2mmHg) and diastolic blood pressure (means ranged from 1.0 to 2.5mmHg)
Other Considerations	<ul style="list-style-type: none"> First glucose-lowering agent to show a reduction in cardiovascular (CV) events. The study was conducted in patients with history of CV disease. It is unknown at this time if this is a class effect of the SGLT2 inhibitors or if the findings apply to those without preexisting CV disease. Do not initiate in patients with eGFR < 45mL/min/1.73m² High cost (SGLT2 inhibitors are approximately \$200+/month)

Background

Purpose for Review

The purpose of this monograph is to evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating empagliflozin (EMP) for possible addition to the VA National Formulary

Other Therapeutic Options	Formulary Alternatives	Other Considerations
	Metformin	First-line agent, adverse GI effects, low risk of hypoglycemia, inexpensive
	Glipizide	Hypoglycemia, weight gain, inexpensive
	Saxagliptin	Modest A1C lowering, weight neutral, low risk of hypoglycemia
	NPH/glargine and/or detemir	Injection, potential to titrate to A1C goal, hypoglycemia, weight gain
	Regular/aspart	Injection, potential to titrate to A1C goal, hypoglycemia, weight gain, complex dosing
	Acarbose	Modest A1C lowering, adverse GI effects, frequent dosing
	Non-formulary Alternatives	Other Considerations
	GLP-1 agonists	Injection, adverse GI effects, low risk of hypoglycemia, weight loss, pancreatic adverse effects?, expensive
	TZDs	Weight gain, edema, heart failure, bone fracture
	SGLT2 inhibitors	Modest A1C lowering, GU infections, volume-depletion related AEs, weight loss, expensive
	Meglitinides	Hypoglycemia, weight gain, frequent dosing

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to August 2015) using the search term empagliflozin. The search was limited to studies performed in humans and published in the English language.

Review of Efficacy

This review is limited to Phase 3 trials and the approved doses empagliflozin 10mg and 25mg. The trials range in duration from 12-104 weeks ([Appendix 1](#)). Several of the 12-24week trials have 78-week extension data available ([Table 1](#)). The majority of primary trials compare empagliflozin to placebo and 2 have an active comparator (sitagliptin and glimepiride). Two trials evaluate monotherapy and the others are add-on to other diabetes drugs. There are 3 trials conducted in special populations (chronic kidney disease, hypertension, and obese patients) and a long-term cardiovascular safety trial

Glycemic Efficacy

Average baseline A1C ranged between 7.9%-8.3%. The mean A1C for most studies was approximately 8.0%; patients enrolled in the add-on to insulin trial had higher baseline averages (A1C 8.3%). Rescue therapy with another anti-glycemic agent was allowed for most trials as defined by protocol.

In Kovacs et al, 75.5% of patients were on pioglitazone + metformin; the remainder was taking pioglitazone alone. For the comparator study by Ridderstrale et al., the mean daily dose of glimepiride was 2.7mg (maximum approved dose 8mg). The baseline mean daily dose of insulin in study 33 was approximately 47units. In the trial of obese patients by Rosenstock et al., 71% were taking metformin in addition to multi-dose insulin. The mean baseline basal and prandial insulin doses were approximately 50 and 40 units respectively. Insulin doses for both insulin trials were to remain stable during the first 18 weeks of the study and could be adjusted according to treat-to-target for the remainder of the study. In the chronic kidney disease (CKD) study where study drug was added to baseline treatment, over 50% of patients were using insulin and or SUs.

The mean change in A1C ranged from -0.6 to -0.8% except for the multi-dose insulin trial where the mean change was approximately -1.2%. There was very little difference between the 10mg and 25mg doses (approximately 0.1% difference). An A1C <7% was achieved by 24-38% of patients receiving empagliflozin 10mg and 30-44% receiving 25mg. Changes in fasting plasma glucose (FPG) followed a similar pattern. Improvement in A1C was similar for sitagliptin and empagliflozin (monotherapy study) and glimepiride and empagliflozin (add-on to metformin); however, there was less improvement in FPG with sitagliptin or glimepiride relative to empagliflozin. [Appendix 1](#)

Fewer patients receiving empagliflozin required rescue therapy compared to placebo. Need for rescue was similar for empagliflozin and sitagliptin and significantly less with empagliflozin compared to glimepiride.

In the insulin trials, the mean change in insulin dose between weeks 18-78 in the basal insulin ± metformin/SU trial was -1.21, -0.47, and 5.45 units for EMP10, EMP25, and placebo respectively. For the multidose dose insulin trial, the mean change in total daily dose (basal+prandial) was 1.3, -1.1, and 10.2 units for EMP10, EMP25, and placebo respectively.

The dedicated renal impairment study evaluated improvement in A1C according to baseline renal function. The change in A1C for empagliflozin 25mg and placebo respectively was -0.63% and 0.06% (eGFR 60 to < 90); -0.37% and 0.05% (eGFR ≥30 to < 60); 0.04 and -0.18 (eGFR ≥15 to <30). Urinary glucose excretion is proportional to GFR; therefore, it is not unexpected that a lesser response was seen in those with greater renal impairment. Empagliflozin is not approved for use in those with eGFR <45mL/min per 1.73m².

Post-prandial glucose (PPG) was evaluated in a subset of patients in 3 trials. Empagliflozin decreased mean 2-hour PPG by approximately 50mg/dL (add-on to metformin) and 36mg/dL (add-on to metformin+SU). In the head-to-head trial, 2-hour PPG was reduced by 46.4mg/dL (EMP25) and 32.4mg/dL (glimepiride).

Three of the 24-week placebo-controlled trials included an open-label empagliflozin arm in a subgroup patients with a baseline A1C >10%. The mean change in A1C was -3.7% (monotherapy), -3.23% (add-on to metformin), and -2.89% (add-on to metformin +SU).

The extension trials from 4 of the placebo-controlled trials show the A1C lowering effect is maintained (**Table 1**). In addition, extension data were available for two 12-week Phase 2b dose-finding trials with active comparator arms. In the monotherapy study, the reduction in A1C was numerically greater with metformin. The add-on to metformin study showed numerically greater reduction in A1C with EMP25 compared to EMP10 and sitagliptin.

Table 1: Extension trials: Selected Outcomes

Study	Duration	Treatment arms	n	Baseline A1C (%)	A1C (%) ^	Baseline weight (kg)	Weight change (kg)^	SBP/DBP^ (mmHg)
Haring 2014	76 weeks	EMP10 + MET	217	7.9	-0.61*	82	-1.9*	-4.4*/-2.0*
		EMP25+ MET	213	7.9	-0.73*	82	-2.2*	-3.7*/-1.4
		PBO + MET	207	7.9	-	80	-	-
Haring 2013	76 weeks	EMP10 + MET +SU	225	8.1	-0.72*	77	-1.8*	-2.2*/-1.1
		EMP25+ MET +SU	216	8.1	-0.69*	78	-1.6*	-2.1*/-0.9
		PBO + MET+SU	225	8.2	-	76	-	-
Kovacs 2014	76 weeks	EMP10+PIO ±MET	165	8.1	-0.59*	78	-2.0*	-2.0/-1.5
		EMP25+PIO ±MET	168	8.1	-0.69*	79	-1.7*	-3.7*/-2.2*
		PBO+PIO ±MET	165	8.2	-	78	-	-
Study 33	78 weeks	EMP10+BI±MET/SU	169	8.3	-0.46*	92	-3.0*	-4.2*/na
		EMP25+BI±MET/SU	155	8.3	-0.62*	95	-3.0*	-2.5/na
		PBO+BI±MET/SU	170	8.2	-	90	-	-
Ferrannini 2013¶	78 weeks	EMP10	106	7.9	-0.34	83	-2.2	0.1/-1.6
		EMP25	105	8.0	-0.47	84	-2.6	-1.7/-2.2
		MET	56	8.2	-0.56	86	-1.3	2.0/-0.6
Ferrannini 2013¶	78 weeks	EMP10+MET	166	7.9	-0.34	91	-3.1	-3.3/-0.9
		EMP25+MET	166	7.9	-0.63	90	-4.0	-3.0/-2.0
		SIT+MET	56	8.0	-0.40	89	-0.4	1.8/1.2

*Significant vs. placebo

^Treatment difference (EMP-PBO) shown for both Haring and Kovacs studies and Study 33

¶Open-label extension from 12-week Phase IIb dose-finding trial

Abbreviations: BI=basal insulin; DBP=diastolic blood pressure; EMP=empagliflozin; MET=metformin; na=not applicable; PBO=placebo; PIO=pioglitazone; SBP=systolic blood pressure; SU=sulfonylurea

Glycemic control was evaluated in the long-term CV trial. The treatment difference vs. placebo for EMP10 and EMP25 respectively was -0.54% and -0.6% (week 12), -0.42% and -0.47% (week 94), and -0.24% and -0.36% (week 2016).

Weight

The urinary loss of glucose using SGLT2 inhibitors has been estimated to be 60-80g daily, which equates to approximately 200-300 kcal/day. There was significantly greater weight loss with empagliflozin compared to placebo. The magnitude of loss decreased when combined with drugs known to cause weight gain (SUs, TZDs, insulin). More patients randomized to empagliflozin had $\geq 5\%$ decrease in weight (**Appendix 1**).

In the empagliflozin vs. glimepiride trial, change in weight was -3.1kg and 1.3kg for respectively; 27.5% of EMP25 patients achieved $\geq 5\%$ weight loss compared to 3.8% in the glimepiride group. In the monotherapy trial, there was significantly greater weight loss with empagliflozin (-2.4kg) than sitagliptin (0.2kg).

The 76-78 week extension trials from 4 of the placebo-controlled trials show the reduction in weight persists (**Table 1**). The extension data for two 12-week Phase 2b dose-finding trials show greater weight reduction with empagliflozin compared to metformin or sitagliptin.

Blood Pressure

Decrease in mean systolic blood pressure (SBP) ranged from 2.9 to 5.2mmHg. Decrease in mean diastolic blood pressure (DBP) ranged from 1.0 to 2.5mmHg (**Appendix 1**).

A dedicated 12-week hypertension study was conducted in patients receiving up to 2 antihypertensive medications. Patients with mean seated BP $\geq 160/100$ mmHg were excluded. The percentage of patients taking 1 or 2 antihypertensive medications at baseline was 43% and 47% respectively. The dose of baseline antihypertensive medications was to remain unchanged if possible. Mean baseline SBP was 142mmHg (office measurement) and 131mmHg (ambulatory 24h monitoring). Mean baseline DBP was 84mmHg and 75mmHg respectively for office and ambulatory measurements.

The change in 24-h SBP and DBP was greater with empagliflozin compared to placebo. The change in daytime measurements was greater than the nighttime measurements and greater with office measurements than the ambulatory measurements. Mean 24-h BP was also analyzed according to those with BP $\geq 130/80$ and $< 130/80$. Those with BP $\geq 130/80$ had a greater change than those with BP $< 130/80$ (**Table 2**).

Table 2: Blood Pressure Results from 12-week Hypertension Study

	EMP10	EMP25	PBO
24-h ambulatory SBP/DBP (mmHg)	-2.95/-1.04	-3.69/-1.40	0.48/0.32
Seated office measurement SBP/DBP (mmHg)	-4.6/-3.06	-5.47/-3.02	-0.67/-1.13
Daytime ambulatory SBP/DBP (mmHg)	-3.42/-1.24	-4.25/-1.67	0.53/0.32
Nighttime ambulatory SBP/DBP (mmHg)	-2.10/-0.65	-2.50/-0.84	0.41/0.31
24-h ambulatory SBP/DBP in those with BP $\geq 130/80$ (mmHg)	-5.47/-2.57	-6.33/-2.56	-1.30/-0.72
24-h ambulatory SBP/DBP in those with BP $< 130/80$ (mmHg)	-0.25/0.49	-0.22/0.22	2.44/1.52

The extension trials from 4 of the placebo-controlled trials show that the reduction in BP persists (**Table 1**). The extension data for two 12-week Phase 2b dose-finding trials show greater BP reduction with empagliflozin compared to metformin or sitagliptin.

Cardiovascular Outcomes

EMPA-REG OUTCOME evaluated CV outcomes and mortality in patients with type 2 diabetes. Patients (n=7034) with established CV disease (e.g., history of MI, CAD, CABG, history of stroke, peripheral occlusive arterial disease, unstable angina) were randomized to empagliflozin 10mg, 25mg or placebo in addition to their usual diabetes drugs. Randomization was stratified according to baseline A1C, BMI, geographic region, and renal

function. The primary endpoint was the composite of cardiovascular (CV) death, nonfatal myocardial infarction (MI), and nonfatal stroke.

Approximately 71% of patients were male and 72% white. Baseline diabetes medications were as follows: approximately 74% metformin, 48%, insulin (median daily dose 53 units), SU 43%, DPP4 inhibitor 11%, TZD 4.3%, and GLP-1 agonist 2.8%. Approximately 30% were on monotherapy and 49% on dual therapy.

Prior CV events were as follows: MI (47%), CAD (76%), CABG (25%), stroke (23%), and POAD (21%). Cardiac medications included aspirin (85%), statins (77%), fibrates (0%), beta-blockers (64%), RAS blocking agents (80%), and calcium channel blockers (30%).

Mean baseline values were A1C 8.1%, BMI 30.6, weight 86.4kg, SBP/DBP 135/77mmHg, and eGFR 74(22%, 52% and 26% had eGFR >90, 60 to <90, and 30 to <60 respectively).

The median treatment duration was 2.6 years and the median observation time was 3.1 years. The percentage of patients who had a primary composite outcome event was significantly lower with empagliflozin than placebo (**Table 6**). This outcome was driven by a reduction in CV mortality as the difference for nonfatal MI and stroke was not significant. Other secondary outcomes that showed a significant reduction in events were all-cause mortality and hospitalization for heart failure.

Several factors remain unknown at this time, including the mechanism explaining these findings, whether benefits extend to those without underlying CV disease, and if this is a class effect of the SGLT2 inhibitors.

Table 6: Results of Long-Term Cardiovascular Trial

	Empagliflozin % (rate per 1000 pt-yr)	Placebo % (rate per 1000 pt-yr)	Hazard ratio [95%CI]; p-value
Primary outcome			
CV death, nonfatal MI, nonfatal stroke	10.5 (37.4)	12.1 (43.9)	0.86 [0.74, 0.99]; p=0.04
Key 2° outcome			
Primary outcome + hospitalization for unstable angina	12.8 (46.4)	14.3 (52.5)	0.89 [0.78, 1.01]; p=0.08
All- cause mortality	5.7 (19.4)	8.3 (28.6)	0.68 [0.57, 0.82]; p<0.001
CV mortality	3.7 (12.4)	5.9 (20.2)	0.62 [0.49, 0.77]; p<0.001
Nonfatal MI	4.5 (16.0)	5.2 (18.5)	0.87 [0.70, 1.09]; p=0.22
Nonfatal stroke	3.2 (11.2)	2.6 (9.1)	1.24 [0.92, 1.67]; p=0.16
Hospitalization for unstable angina	2.8 (10.0)	2.8 (10.0)	0.99 [0.74, 1.34]; p=0.97
Hospitalization for HF	2.7 (9.4)	4.1 (14.5)	0.65 [0.50, 0.85]; p=0.002

Potential Off-Label Use

Type 1 diabetes

Safety

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	None
Contraindications	<ul style="list-style-type: none"> History of serious hypersensitivity reaction to empagliflozin Severe renal impairment, end-stage renal disease, or dialysis
Warnings/Precautions	<i>Hypotension:</i> Empagliflozin causes intravascular volume contraction. Symptomatic hypotension may occur after initiation of empagliflozin particularly in patients with renal impairment, elderly

patients, patients with low systolic blood pressure and those taking diuretics. Volume status should be assessed and corrected before initiating empagliflozin in patients with these characteristics. Monitor for signs and symptoms after initiating therapy and increase monitoring in clinical situations where volume contraction is expected.

Impairment in renal function: Empagliflozin increases serum creatinine and decreases eGFR. The risk of impaired renal function is increased in elderly patients and patients with moderate renal impairment. Evaluate renal function prior to initiating empagliflozin and periodically thereafter.

Hypoglycemia with concomitant use with insulin or insulin secretagogues: The risk of hypoglycemia can be increased when empagliflozin is combined with insulin or insulin secretagogues (e.g., sulfonylureas). A lower dose of insulin or insulin secretagogue may be needed to minimize the risk.

Genital mycotic infections: Empagliflozin increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections. Monitor and treat as appropriate.

Urinary tract infections: empagliflozin increases the risk for UTI. Monitor and treat as appropriate.

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

**Safety
Considerations**

Hypoglycemia

Overall hypoglycemia was defined as blood glucose ≤ 70 mg/dL. Severe hypoglycemia was defined as an episode requiring the assistance of another person regardless of blood glucose.

The incidence of hypoglycemia was low and similar to placebo when empagliflozin is used as monotherapy or in combination with metformin, or pioglitazone. The incidence of hypoglycemia is higher when combined with other drugs known to cause hypoglycemia such as SUs or insulin (**Appendix 2**). In the insulin trials, although the incidence of hypoglycemia was increased, the combination with empagliflozin was comparable to the placebo + insulin \pm orals arms.

In the 104-week trial of empagliflozin vs. glimepiride, the incidence of hypoglycemia was 2% and 24% respectively.

Severe hypoglycemia with empagliflozin was uncommon and reported only in the insulin and CKD (approximately 35% using insulin) trials.

The incidence of hypoglycemia in the extension trials follows a similar pattern to the parent trial (**Table 3**).

Table 3: Extension trials: Selected Outcomes

Study	Duration	Treatment arms	n	Hypoglycemia¶	UTI	Genital infections
Haring 2014	76 weeks	EMP10 + MET	217	4.1	14.3	8.3
		EMP25+ MET	213	4.2	10.3	9.3
		PBO + MET	207	3.4	13.6	0.5
Haring 2013	76 weeks	EMP10 + MET +SU	225	23.7	17.0	4.5
		EMP25+ MET +SU	216	19.4	16.1	6.0
		PBO + MET+SU	225	15.6	16.0	0.9
Kovacs 2014	76 weeks	EMP10+PIO ±MET	165	1.8	22.4	10.3
		EMP25+PIO ±MET	168	3.0	22.0	4.2
		PBO+PIO ±MET	165	4.2	26.7	3.0
Study 33	78 weeks	EMP10+BI±MET/SU	169	36.1	14.8	7.7
		EMP25+BI±MET/SU	155	36.1	11.6	5.2
		PBO+BI±MET/SU	170	35.3	8.8	1.8
Ferrannini 2013¶	78 weeks	EMP10	106	0.9	3.8	4.7
		EMP25	105	1.8	6.4	5.5
		MET	56	3.6	3.6	1.8
Ferrannini 2013¶	78 weeks	EMP10+MET	166	1.8	9.0	3.0
		EMP25+MET	166	2.4	12.7	3.6
		SIT+MET	56	3.6	12.5	0

¶Hypoglycemia defined as blood glucose \leq 70mg/dL and/or requiring assistance

Infection

The SGLT2 inhibitors increase urinary glucose excretion; therefore, there is increased potential for fungal growth in perineum and bacterial growth in urinary tract. There is an increased rate of UTIs and genital mycotic infections with empagliflozin compared to placebo/active comparators.

According to pooled results of 5 placebo-controlled trials (Roden, Kovacs, Study 33, and both Haring trials), the incidence of genital mycotic infection in females was 5.4%, 6.4%, and 1.5% for EMP10, EMP25, and placebo respectively. In males, the rate was 3.1%, 1.6%, and 0.4 % respectively. This AE led to discontinuation of study drug in 0.2% of empagliflozin-treated patients versus none in the placebo group.

In the active comparator arms, genital infections occurred more frequently with empagliflozin than glimepiride (2%) or sitagliptin (1%). Results according to individual trials are shown in **Appendix 2**.

The pooled incidence of UTIs in females was 18.4%, 17.0%, and 16.6% for EMP10, EMP25, and placebo respectively. In males, the incidence was 3.6%, 4.1%, and 3.2 % respectively. Patients with chronic or recurrent UTIs were at higher risk of UTI. For both UTI and genital infections, the majority of patients had a single episode of infection. In the overall population, this AE led to discontinuation of study drug in 0.1%, 0.2%, and 0.1% of patients receiving EMP10, EMP25, and placebo respectively. The risk of UTIs is increased in older patients (\geq 75 years old) to 15.7%, 15.1%, and 10.5% respectively and in those with worsening renal function (results not shown).

The overall (male and female) incidence of UTIs and genital infections for the extension trials are shown in **Table 3**.

Volume Depletion

Empagliflozin can cause osmotic diuresis due to increased urinary glucose; therefore, adverse events related to volume depletion (dehydration, hypovolemia, orthostatic hypotension, hypotension, syncope) were evaluated. The pooled incidence in the 5 placebo-controlled trials (Roden, Kovacs, Study 33, and both Haring trials) was 0.5%, 0.3%, and 0.3% respectively in

patients receiving EMP10, EMP25, and placebo.

Patients with impaired renal function, those taking loop diuretics, and the elderly are at higher risk for these events. In the pooled results for the 5 placebo-controlled trials, volume depletion-related AEs in those ≥ 75 years old was 2.3%, 4.4%, and 2.1% for EMP10, EMP25, and placebo respectively.

The safety data base for 18 clinical trials show an increased risk of volume-related AEs for those taking loop diuretics at baseline for empagliflozin versus the comparators (**Table 4**). The risk is less evident for empagliflozin versus comparators when all diuretic use is compared.

Table 4: Volume Depletion Events According to Baseline Diuretic Use

	No diuretics at baseline (n=2528)		Diuretics at baseline (n=1102)		No loop diuretics at baseline (n=3363)		Loop diuretics at baseline (n=267)	
	%	Per 100 pt-yrs	%	Per 100 pt-yrs	%	Per 100 pt-yrs	%	Per 100 pt-yrs
EMP 10	0.9	1.07	2.5	2.76	1.2	1.29	4.9	5.63
EMP25	0.9	0.96	2.7	2.83	1.3	1.36	3.0	3.45
PBO	1.0	1.32	2.2	2.64	1.2	1.59	2.9	3.35
All comparators (including PBO)	0.8	0.95	2.2	2.35	1.1	1.22	2.8	3.11

Data obtained from FDA Medical Review

In the empagliflozin vs. glimepiride trial, there was no difference between groups (1% each) in events consistent with volume depletion.

Dizziness was reported more often with empagliflozin in the multi-dose insulin study (2.7%, 6.9%, and 1.1% for EMP10, EMP25, and placebo respectively).

In the hypertension study, 15.5%, 19.7%, and 16.5% of patients randomized to EMP10, EMP25, and PBO respectively had a positive orthostatic BP test at baseline. At week 12, the orthostatic BP test was positive in 25.95, 29.3%, and 20.1% of patients respectively. One patient each receiving EMP10 and PBO had events consistent with volume depletion.

Results according to individual trials are shown in **Appendix 2**.

Events consistent with volume depletion were assessed in the long-term CV trial. The reported incidence was 4.9%, 5.3%, and 4.9% for EMP10, EMP25, and placebo respectively.

Renal Safety

The pooled results for change in serum creatinine (SCr) and eGFR for the four 24-week placebo-controlled trials are shown in **Table 5**. There was a small increase in mean SCr and decrease in mean eGFR in the empagliflozin groups at week 24.

Results from the CKD study for those with moderate renal impairment are also shown. Baseline SCr and eGFR was approximately 1.5mg/dL and 45ml/min/1.73m² respectively. This group had greater change in renal function compared to those in the pooled trials; the changes were similar at weeks 24 and 52.

Change in eGFR by trial is shown in **Appendix 2**.

Table 5: Serum Creatinine and Estimated Glomerular Filtration Rate

		Renal parameter*	EMP10 (n=830)	EMP25 (n=822)	PBO (n=825)
Four 24-week placebo-controlled trials	Baseline	eGFR	87.1	87.8	87.3
		SCr	0.85	0.85	0.84
	Week 24	eGFR	-0.6	-1.4	-0.3
		SCr	0.01	0.01	0.00
			EMP10	EMP25 (n=187)	PBO (n=187)
Renal impairment Study (eGFR 30-<60)	Baseline	eGFR	NA	45.4	44.3
		SCr		1.46	1.49
	Week 24	eGFR	NA	-3.2	0.2
		SCr		0.12	0.01
	Week 52	eGFR	NA	-2.8	-0.3
		SCR		0.11	0.02

*eGFR (ml/min/1.73m²); SCr (mg/dL)

In the long-term CV safety trial, acute renal failure was reported in 5.2%, 5.3%, and 6.6% of patients in the EMP10, EMP25, and placebo groups respectively. The incidence of acute renal injury was 1.1%, 0.8%, and 1.6% respectively. The change in SCr and eGFR were similar between empagliflozin and placebo. The full analysis on renal outcomes has not yet been performed.

Urine albumin/creatinine ratio (ACR) was assessed in the CKD trial and the empagliflozin vs. glimepiride trial. In the CKD trial, fewer patients receiving empagliflozin 25mg compared to placebo progressed from no albuminuria to microalbuminuria and microalbuminuria to macroalbuminuria. For example in stage 3 CKD 12.2% and 22.2% of patients receiving EMP25 and placebo respectively had a shift from no albuminuria to microalbuminuria and 2.0% and 11.4% respectively had a shift from microalbuminuria to macroalbuminuria.

Similarly, more patients receiving empagliflozin shifted from a higher category to a lower category of albuminuria. In those with stage 3 CKD, 32.6% of those receiving empagliflozin and 8.6% placebo shifted from macroalbuminuria to microalbuminuria. The shift from micro- to no albuminuria was 27.5% and 21.4% respectively.

In the empagliflozin vs. glimepiride trial, there was a decrease in the ACR with empagliflozin and an increase with glimepiride.

Increase in hematocrit

Based on 4 placebo-controlled trials, the hematocrit increased by a median of 2.8% each for EMP10 and EMP25 and decreased by 1.3% in the placebo groups. At the end of treatment, 2.7%, 3.5%, and 0.6% of those who had normal values at baseline, had values above the upper range of normal respectively. The increases appear to be reversible upon discontinuation of empagliflozin.

In the long-term CV study, the mean change in hematocrit from baseline was 4.8%, 5.0%, and 0.9% for EMP10, EMP25, and placebo respectively.

Effect on lipids

According to pooled data from the placebo-controlled trials, LDL-C (baseline value ~90mg/dL) increased by 4.6%, 6.5%, and 2.3% of patients receiving EMP10, EMP25, and placebo respectively. In the sitagliptin arm of the Roden trial, LDL-C increased by 1%. In the EMP25 vs. glimepiride study, LDL-C increased by 7.9% and 1.7% respectively.

Bone Safety

A higher rate of bone fractures, most commonly upper extremity fractures, has been reported with canagliflozin, another SGLT2 inhibitor.

According to the safety database for empagliflozin, fractures occurred with similar frequency between empagliflozin (1.3%) and comparators (1.5%). There was no difference frequency among treatment group for fractures according to small vs large bones or upper vs lower extremities.

The long-term CV trial evaluated bone fractures as a safety outcome. There was no difference between empagliflozin and placebo. The incidence was 3.9%, 3.7%, and 3.9% for EMP10, EMP25, and placebo respectively. It is not known if the risk changes with use beyond 3 years.

Malignancy

In the clinical trials of another SGLT2 inhibitor, dapagliflozin, an imbalance of bladder cancers was observed. The labeling for dapagliflozin states it should not be used with active bladder cancer and used with caution in those with a prior history.

In the empagliflozin safety database of 18 trials, the incidence of all malignancies was 1.02%, 1.11%, 0.91%, and 0.90% for EMP10, EMP25, placebo, and all comparators. The incidence when evaluated according to those with an onset 6 or more months after initiation of study drug was 0.61%, 0.54%, 0.45%, and 0.53% respectively.

There was a numeric imbalance not favoring empagliflozin for lung neoplasms and malignant melanoma. There were 6 cases of lung neoplasms in the empagliflozin group and none in the comparators; one case was primary colon which metastasized to the lung. Patients were current or prior smokers. It was noted that the lung malignancies were of differing cell types which is not typical for drug-associated malignancy.

There were 6 cases of melanoma in the empagliflozin group and none among the comparators. Two patients had prior melanoma, one had multiple prior skin cancers, and one had sun-damaged skin.

Diabetic ketoacidosis

The FDA has issued a warning that the SGLT2 inhibitors canagliflozin, dapagliflozin, and empagliflozin may lead to ketoacidosis. A search of the FDA Adverse Event Reporting System (FAERS) database identified 20 cases of acidosis reported as diabetic ketoacidosis (DKA), ketoacidosis, or ketosis in patients treated with SGLT2 inhibitors from March 2013 to June 6, 2014. Since June 2014, they have continued to receive additional FAERS reports for DKA and ketoacidosis in patients treated with SGLT2 inhibitors.

Atypically, glucose levels were only mildly elevated at less than 200 mg/dL in some reports (patients with type 1 diabetes who have DKA usually have glucose levels above 250 mg/dL; DKA does not routinely occur in patients with type 2 diabetes). Half of the cases reported potential triggers for DKA, including acute illness or recent significant changes such as infection, urosepsis, trauma, reduced caloric or fluid intake, and reduced insulin dose. All cases resulted in emergency room visits or hospitalization to treat the acidosis.

The FDA is continuing to investigate this safety issue and will determine whether changes are needed in the prescribing information.

Patients should pay close attention for any signs of ketoacidosis and seek medical attention immediately if they experience symptoms such as difficulty breathing, nausea, vomiting, abdominal pain, confusion, and unusual fatigue or sleepiness. Health care professionals should

evaluate for the presence of acidosis, including ketoacidosis, in patients experiencing these signs or symptoms; discontinue SGLT2 inhibitors if acidosis is confirmed; and take appropriate measures to correct the acidosis and monitor sugar levels.

Adverse Reactions

Common adverse reactions The following most common adverse events (**Table 7**) are pooled from the four 24-week and one 18-week placebo controlled trials (Roden, Haring 2013, Haring 2014, Ridderstrale, study 33). Hypoglycemia, urinary tract and genital infections are not included here and are discussed separately.

Table 7: Adverse Events Reported in ≥2% of Patients Treated with Empagliflozin and Greater than Placebo (%)

	EMP10 (n=999)	EMP25 (n=977)	PBO (n=995)
URI	3.1	4.0	3.8
↑ urination	3.4	3.2	1.0
Dyslipidemia	3.9	2.9	3.4
Arthralgia	2.4	2.3	2.2
Nausea	2.3	1.1	1.4

Adverse events in the head-to-head empagliflozin and glimepiride trial were generally balanced; events reported more often with glimepiride were hypoglycemia (25% vs. 4%), hyperglycemia (22% vs. 14%), and hypertension (10% vs. 5%). Sitagliptin was an active comparator arm in the Roden trial. Dyslipidemia was reported in 3% of patients receiving sitagliptin.

Death/Serious adverse reactions See **Appendix 2**

Discontinuations due to AEs See **Appendix 2**

Drug Interactions

Drug-drug interactions

- No clinically relevant pharmacokinetic interactions based on *in vitro* and *in vivo* testing.
- Coadministration with diuretics results in increased urine volume and frequency of voids
- Coadministration with insulin or insulin secretagogues increases the risk for hypoglycemia

Drug-food interactions None

Drug-lab interactions Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control

Monitoring glycemic control with 1, 5-AG assay is not recommended as measurements of 1, 5-AG is unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control

Risk Evaluation

As of 9/24/15

Sentinel event advisories

None
Sources: ISMP, FDA, TJC

Look-alike/sound-alike error potentials

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Empagliflozin 10, 25 mg tab	None	None	None	Canagliflozin Dapagliflozin Empagliflozin and linagliptin Empagliflozin and metformin
Jardiance	None	None	None	Januvia Synjardy

- **High alert medication:** The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error
- Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Other Considerations

- First glucose lowering agent to reduce CV events.
- Will need to wait for results of the CV trials for canagliflozin and dapagliflozin to see if this is a class effect.

Dosing and Administration

- The recommended dose is 10 mg once daily in the morning, taken with or without food. In patients tolerating empagliflozin, the dose may be increased to 25 mg.
- In patients with volume depletion, correcting this condition prior to initiation is recommended
- Assessment of renal function is recommended prior to initiation of empagliflozin and periodically thereafter.
- Empagliflozin should not be initiated in patients with an eGFR < 45 mL/min/1.73 m²
- No dose adjustment is needed in patients with an eGFR ≥ 45 mL/min/1.73 m²
- Discontinue empagliflozin if eGFR is persistently < 45 mL/min/1.73 m²

Special Populations (Adults)

	Comments
Elderly	<ul style="list-style-type: none"> • A total of 2721 (32%) patients treated with empagliflozin were 65 years of age and older, and 491 (6%) were 75 years of age and older. • Dosage adjustment is not recommended based on age • There is diminished efficacy in elderly patients with renal impairment • The risk of volume depletion-related adverse reactions increased in patients who were ≥75 years of age to 2.3%, 4.4%, and 2.1% for EMP10mg, EMP 25mg and placebo, respectively • The risk of urinary tract infections increased in patients who were ≥75 years of age to 15.7%, 15.1%, and 10.5% in patients randomized EMP10mg, EMP 25mg and placebo, respectively
Pregnancy	There are no adequate well-controlled studies in pregnant women. In animal studies, renal development and maturation may be affected. In rats, malformation of limb bones increased in fetuses at doses 154x maximum human dose. Reduced body weight was observed in offspring at 4x the maximum clinical dose. During pregnancy, consider alternative treatments especially during the 2 nd and 3 rd trimesters.
Lactation	Empagliflozin is secreted in milk of lactating rats with levels up to 5x that in maternal plasma. It is not known if empagliflozin is excreted in human milk. Data in juvenile rats showed risk to the developing kidney during maturation.

	In humans, kidney maturation occurs <i>in utero</i> and in the first 2 years of life. Because of the potential for serious adverse reactions to the nursing infant, a decision should be made to discontinue empagliflozin or nursing taking into account the importance of the drug to the mother.
Renal Impairment	Glycemic efficacy is decreased in patients with worsening renal function. Risk of adverse reactions (i.e., risk of renal impairment, volume depletion, UTIs) is increased in patients with worsening renal function.
Hepatic Impairment	In subjects with mild, moderate, and severe hepatic impairment according to the Child-Pugh classification, AUC of empagliflozin increased by approximately 23%, 47%, and 75%, and Cmax increased by approximately 4%, 23%, and 48%, respectively, compared to subjects with normal hepatic function. Empagliflozin may be used in patients with hepatic impairment
Pharmacogenetics/genomics	No data identified

Summary

Empagliflozin is the third SGLT2 inhibitor available in the US. Average change in A1C is generally < 1.0%.

Based on the clinical trial data, increasing the dose of empagliflozin from 10mg to 25mg does not appear to offer additional meaningful efficacy. In the active comparator trial, the efficacy of empagliflozin was found to be similar to glipizide and sitagliptin.

Advantages of empagliflozin include low risk of hypoglycemia and weight loss. Most recently, empagliflozin was found to be the first diabetes drug to show a cardiovascular risk reduction. The study was conducted in patients with a history of CV disease. Whether this finding is unique to empagliflozin or is a class effect of the SGLT2 inhibitors is not known. Results for the cardiovascular outcomes trials for canagliflozin and dapagliflozin are expected in 2017 and 2019 respectively. It is unknown if the findings of the empagliflozin CV study applies to patients without preexisting CV disease.

Adverse reactions most likely attributed to SGLT2 inhibitor mechanism of action include increased incidence of genital mycotic infections, UTIs, osmotic diuresis and reduced intravascular volume related events.

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Appendix 1: Selected Outcomes

Study	Duration	Patients	Treatment arms	n	BL A1C (%)	A1C (%)	A1C < 7% (%pts)	BL FPG (mg/dL)	FPG (mg/dL)	Rescue (%)	BL weight (kg)	Weight change (kg)	Weight loss ≥5% (%pts)	SBP/DBP (mmHg)
Roden 2013	24 weeks	No DM tx for 12 weeks	EMP10	224	7.9	-0.66*	35.3	153	-19*^	1.3	78.4	-2.3*^	23*^	-2.9*^/-1.0^
			EMP25	224	7.9	-0.78*	43.6	153	-25*^	0.9	77.8	-2.5*^	29*^	-3.7*^/-1.9*^
			SIT 100	223	7.9	-0.66*	37.5	147	-7	0.9	79.3	0.2	6	0.5/0.7
			PBO	228	7.9	0.08	12.0	155	12	14.5	78.2	-0.3	4	-0.3/-0.5
Haring 2014	24 weeks**	Inadequate control on MET	EMP10 + MET	217	7.9	-0.70*	37.7*	155	-20.0*	5.5	81.6	-2.1*	21.2*	-4.5*^/-2.0*
			EMP25+ MET	213	7.9	-0.77*	38.7*	149	-22.3*	3.3	82.2	-2.5*	23*	-5.2*^/-1.6*^
			PBO + MET	207	7.9	-0.13	12.5	156	6.4	14.0	79.7	-0.5	4.8	-0.4/0.0
Haring 2013	24 weeks**	Inadequate control on MET+SU	EMP10 + MET +SU	225	8.1	-0.82*	26.3*	151	-23.3*	2.2	77.1	-2.2*	27.8*	-4.1*^/-2.1
			EMP25+ MET +SU	216	8.1	-0.77*	32.2*	156	-23.3*	0.9	77.5	-2.4*	23.6*	-3.5*^/-2.2
			PBO + MET+SU	225	8.2	-0.17	9.3	152	5.5	11.6	76.2	-0.4	5.8	-1.4/-1.8
Kovacs 2014	24 weeks**	Inadequate control on PIO ±MET	EMP10+PIO ±MET	165	8.1	-0.59*	23.8*	152	-17.0*	Not shown	78.0	-1.6*	18.8*	-3.1*^/-1.5*
			EMP25+PIO ±MET	168	8.1	-0.72*	30.0*	152	-22.0*		78.9	-1.5*	13.7*	-4.0*^/-2.2*
			PBO+PIO ±MET	165	8.2	-0.11	7.7	152	6.5		78.1	-0.3	5.5	0.7/0.3
Ridderstrale 2014	104 weeks	Inadequate control on MET	EMP25+MET	765	7.9	-0.66	34	150	-15.3^	14.8^	82.5	-3.1^	27.5^	-3.1*^/-1.8^
			GLM (mean dose 2.7mg) +MET	780	7.9	-0.55	31	150	-3.1	23.7	83.0	1.3	3.8	2.5/0.9
Study 33	18 weeks**	Inadequate control on insulin (mean 47U) ±orals	EMP10+BI±MET/SU	169	8.3	-0.57*	30*	138	-17*		92	-2.1*		
			EMP25+BI±MET/SU	155	8.3	-0.71*	30*	146	-23*	?	95	-0.9	na	See 72 week data
			PBO+BI±MET/SU	170	8.2	-0.01	9	142	11		90	-0.05		
Rosenstock 2014	52 weeks**	Inadequate control on MDI (>60U/d)± MET	EMP10+MDI±MET	186	8.4	-1.18*	31.4*	150	-23.8*		96.7	-1.95*		-3.4/-1.2
			EMP25+MDI±MET	189	8.3	-1.27*	41.7*	150	-25.7*		95.9	-2.04*	na	-3.8/-2.5^
			PBO+MDI±MET	188	8.3	-0.81	21.0	151	-11.3		95.5	0.44		-2.9/-0.5
Barnett 2014¶	24 weeks	CKD study Add-on to existing meds	EMP10+ BL meds	98/na	8.0	-0.46*/na	17/na	146/na	-13.9/na	2.0/na	92/na	-1.8/na	11.2/na	
			EMP25+ BL meds	97/187	8.0	-0.63*^/-0.37	24.2/12	148/142	-18.1/-9.0	2.1/8.0	88/83	-2.3/-1.0	23.7/10.7	See footnote§
			PBO+BL meds	95/187	8.0	0.06/0.05	6.7/7.9	144/144	5.7/10.8	18.9/12.3	86/83	-0.3/-0.1	2.1/4.3	
Tikkanen 2015^^	12 weeks	Hypertension study (taking up to 2 anti-HTN drugs)	EMP10	276	7.9	-0.59*		157	-16.6*	1.4	NS (mean BMI 32.6)	-1.68*		-4.6*^/-3.06*
			EMP25	276	7.9	-0.62*	na	162	-23.0*	2.9		-2.16*	na	-5.4*^/-3.02*
			PBO	271	7.9	0.03		160	7.2	2.6		-0.18		-0.67/-1.13

*significant vs. placebo; ^significant vs. active comparator; ** Extension data available

¶Values for renal impairment study shown according to eGFR subgroups (eGFR ≥60 to <90/eGFR ≥30 to <60); Empagliflozin was not effective in the subgroup with eGFR ≥15 to <30 (values not shown in table)

§Change in SBP/DBP (mmHg) for those with eGFR ≥60 to <90: -2.9/-1.4 (EMP10), -4.5/-2.2 (EMP25), 0.7/1.1 (PBO). Change in SBP/DBP (mmHg) for those with eGFR ≥30 to <60: -3.9/-1.7 (EMP25), 0.4/0.2 (PBO)

^^change in SBP/DBP are seated office values; values for ambulatory BP monitoring are discussed in text

Abbreviations: BI=basal insulin; BL=baseline; CKD=chronic kidney disease; DBP=diastolic blood pressure; EMP=empagliflozin; FPG=fasting plasma glucose; GLM=glimepiride; MDI=multiple dose insulin; MET=metformin; na=not applicable; NS=not shown; PBO=placebo; PIO=pioglitazone; SBP=systolic blood pressure; SIT=sitagliptin; SU=sulfonylurea

Appendix 2: Select Adverse Events

Study	Duration	Treatment arms	n	d/c due to AE	≥ 1SAE	Deaths (n)	Overall hypoglycemia‡	Severe hypoglycemia ‡	UTI Male/female	Genital infection Male/female	eGFR (mL/min/1.73 ²)
Rodén 2013	24 weeks	EMP10	224	1	4	0	0.4	0	2/15	3/4	0.65
		EMP25	224	2	2	0	0.4	0	1/13	1/9	1.30
		SIT 100	223	2	3	0	0.4	0	3/9	1/1	-1.76
		PBO	228	3	3	1	0.4	0	2/9	0/0	-0.02
Haring 2014	24 week	EMP10 + MET	217	0.9	3.2	0	1.8	0	0/12	0.8/7.6	0.1
		EMP25+ MET	213	2.3	2.3	0	1.4	0	0.8/11.8	0.8/9.7	-1.7
		PBO + MET	207	3.4	3.4	0	0.5	0	2.6/7.7	0/0	1.0
Haring 2013	24 weeks	EMP10 + MET +SU	225	2.7	4.9	1	16.1	0	2.7/18	0.9/4.5	-1.3
		EMP25+ MET +SU	216	3.2	0.5	0	11.5	0	0/17.5	0.9/3.9	-2.5
		PBO + MET+SU	225	3.6	6.2	0	8.4	0	2.7/13.3	0.9/0.9	-1.9
Kovacs 2014	24 weeks	EMP10+PIO ±MET	165	1.2	4.2	0	1.2	0	3.6/30.5	7.2/9.2	-2.1
		EMP25+PIO ±MET	168	3.0	3.6	2	2.4	0	2.4/21.7	1.2/6.0	-3.4
		PBO+PIO ±MET	165	2.4	4.2	1	1.8	0	8.2/22.8	1.4/3.3	-0.5
Ridderstrale 2014	104 weeks	EMP25+MET	765	5	9	5	2		7/22	9/15	1.7
		GLM (mean dose 2.7mg) +MET	780	4	9	5	24	NR	5/23	1/3	-1.8
Study 33	18 weeks	EMP10+BI±MET/SU	169	11.2	16.6	0	37.9	0	14.8	7.7	Similar in 3 treatment groups
		EMP25+BI±MET/SU	155	12.9	18.1	0	39.4	1.3	11.6	5.2	
		PBO+BI±MET/SU	170	7.6	16.5	1	37.6	0	8.8	1.8	
Rosenstock 2014	52 weeks	EMP10+MDI±MET	186	5.4	10.8	0	51.1	1.6	5.2/27	1.0/7.9	-1.6
		EMP25+MDI±MET	189	4.8	11.6	1	57.7	0.5	3.6/24.8	8.3/10.5	-1.6
		PBO+MDI±MET	188	4.8	11.7	0	58	1.6	0/25.7	1.3/1.8	-2.0
Barnett 2014¶	52 weeks	EMP10+ BL meds	98/na	4.1/na	6.1/na	0/na	26.5/na	1.0/na			-2.04/na
		EMP25+ BL meds	97/187	4.1/5.3	7.2/11.8	0/0.5	22.7/27.8	1.0/1.6	See footnote§	See footnote^	-2.47/-2.8
		PBO+ BL meds	95/187	5.3/3.2	11.6/12.3	0/0.5	24.2/28.3	0/2.7			-0.71/-0.3
Tikkanen 2015	12 weeks	EMP10	276	1.4	1.1	1	6.5	0	0.6/9.5	4.7/5.7	-0.20
		EMP25	276	2.2	1.4	0	6.2	0	2.6/7.4	3.9/7.4	-2.6
		PBO	271	1.8	2.6	0	4.8	0	0.6/8.7	0.6/0	-0.27
Zinman 2015		EMP10+ BL meds	2345	17.7	37.4	4.1%	28.0	1.4	10.9/35.5	5.4/9.2	-2.3
		EMP25+ BL meds	2342	17.0	39.0	3.4%	27.6	1.3	10.1/37.3	4.6/10.8	-2.9
		PBO+ BL meds	2333	19.4	42.3	5.1%	27.9	1.5	9.4/40.6	1.5/2.6	-2.0

‡ Overall hypoglycemia was defined as blood glucose ≤70mg/dL. Severe hypoglycemia was defined as an episode requiring the assistance of another person regardless of blood glucose

¶ Values for CKD study shown according to eGFR subgroups (eGFR ≥60 to <90/eGFR ≥30 to <60); Empagliflozin was not effective in the subgroup with eGFR ≥15 to <30 (values not shown in table)

§ Incidence of UTIs (male/female) for those with eGFR ≥60 to <90: 8.3/23.7 (EMP10), 3.3/19.4 (EMP25), 8.9/25.6 (PBO). UTIs for those with eGFR ≥30 to <60: 5.6/31.3 (EMP25), 3.8/30.9 (PBO)

^ Incidence of genital infections (male/female) for those with eGFR ≥60 to <90: 10/2.6(EMP10), 0/13.9 (EMP25), 3.6/10.3 (PBO). Genital infections for those with eGFR ≥30 to <60: 1.9/3.8 (EMP25), 0.9/1.2 (PBO)