National PBM Drug Monograph
Dapagliflozin (Farxiga)
VHA Pharmacy Benefits Management Strategic Healthcare Group
Medical Advisory Panel and VISN Pharmacist Executives

The purpose of VACO PBM-SHG drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

EXECUTIVE SUMMARY

- Dapagliflozin (DAP) is the second selective inhibitor of the sodium-glucose co-transporter 2 (SGLT2) to be marketed in the US. Inhibiting SGLT2 at the proximal renal tubule results in reduced reabsorption of filtered glucose and increases urinary glucose excretion.

- It is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes (T2DM). Dapagliflozin has been studied as monotherapy or in combination with metformin (MET), sulfonylureas (SU), pioglitazone (PIO), sitagliptin (SIT) ± metformin and insulin ± other oral agents.

- The recommended starting dose is 5mg taken once daily in the morning with or without food. Assessment of renal function is recommended prior to initiation of dapagliflozin and periodically thereafter. Do not initiate dapagliflozin in patients with eGFR < 60mL/min/1.73m^2. If additional glycemic control is needed, the dose may be increased to 10mg once daily in patients who have an estimated GFR (eGFR) of ≥ 60mL/min/1.73m^2. Discontinue dapagliflozin if eGFR is persistently eGFR < 60mL/min/1.73m^2.

- Dapagliflozin is contraindicated in severe renal impairment, end stage renal disease, or patients on dialysis.

- Duration of the phase 3 trials ranged from 24-52 weeks (extension trials with data up to 48-104weeks). In general, the mean reduction in A1C is <1.0%. Similar to other agents used to treat diabetes, those with higher baseline A1C values had a greater absolute reduction in A1C.

- Use of dapagliflozin monotherapy, or in combination with metformin or sitagliptin resulted in weight loss from baseline. Generally, the magnitude of weight lost was less when dapagliflozin was combined with other agents known to cause weight gain (e.g., SUs, TZDs, insulin).

- There is low incidence of hypoglycemia when dapagliflozin is used as monotherapy or in combination with metformin, pioglitazone, or sitagliptin. When combined with other drugs known to cause hypoglycemia such as insulin or SUs the incidence of hypoglycemia is greater with the addition of dapagliflozin compared to the addition of placebo

- Dapagliflozin is associated with an increased risk of urinary tract (UTI) and genital mycotic infections. Those with a prior history were more likely to have an infection during the trial than those with no prior history.

- Pooled trial data show no increased risk for CV events with dapagliflozin relative to placebo.

- Dapagliflozin can cause osmotic diuresis due to increased urinary glucose. Adverse events related to volume depletion (dehydration, hypovolemia, orthostatic hypotension, and hypotension) were increased with dapagliflozin versus placebo. Older patients, those with eGFR <60mL/min/1.73m^2, and concomitant loop diuretic use were at higher risk.

- Dapagliflozin can cause decrease in eGFR and increase in serum creatinine. Patients with moderate renal impairment were more likely to experience a decrease in eGFR than those with normal or mildly impaired renal function. The decrease in eGFR occurs early in treatment and coincides with reduced intravascular volume due to osmotic diuresis that can occur at that time; however, it tends to trend towards baseline values by week 24.

- There was a dose-dependent decrease in systolic blood pressure with dapagliflozin relative to placebo or active comparator. Mean changes with dapagliflozin across studies ranged from -0.8 to -6.7mmHg; greater decreases were seen in the add-on to sitagliptin and insulin studies. Mean changes in diastolic blood pressure ranged from -1.0 to -3.1mmHg. Symptomatic hypotension may occur after initiation of dapagliflozin particularly in patients with eGFR <60mL/min/1.73m^2, elderly patients, those taking loop diuretics.

- There was an imbalance in the number of bladder cancer and breast cancer reported with dapagliflozin compared to placebo. At this time a causal relationship remains inconclusive. Per product labeling, dapagliflozin should not be used in patients with active bladder cancer and to use with caution in those with a history of bladder cancer.

- Pregnancy Category C; avoid dapagliflozin during pregnancy, especially during the 2nd and 3rd trimesters. Because of potential serious adverse reactions to the nursing infant, a decision should be made to discontinue dapagliflozin or nursing taking into account importance of the drug to the mother.

Introduction

Dapagliflozin was approved in January 2014 and is the second selective inhibitor of the sodium-glucose co-transporter 2 (SGLT2) to be marketed in the US.

Pharmacology

The kidney plays a major role in glucose homeostasis through glomerular filtration and reabsorption of glucose. Renal reabsorption of glucose is mediated by SGLT1 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.

The glycemic lowering effects of SGLT2 inhibitors is independent of insulin secretion by the pancreas; therefore, the efficacy is not expected to decline with progressive ß-cell failure.

FDA approved indications

Dapagliflozin is indicated as an adjunct to diet and exercise to improve glycemic control in patients with T2DM.

Dapagliflozin has been studied as monotherapy or in combination with metformin (MET), sulfonylureas (SU), pioglitazone (PIO), sitaglitptin (SIT) ± metformin and insulin ± other oral agents.

Current VA alternatives

None in the SGLT2 inhibitor class; other drugs for treatment of type 2 diabetes on the VANF include metformin, glipizide, acarbose, saxagliptin, NPH insulin, long-acting insulin analogs, regular insulin, and insulin aspart.

Dosing

- Assessment of renal function is recommended prior to initiation of dapagliflozin and periodically thereafter
- Dapagliflozin should not be initiated in patients with eGFR < 60mL/min/1.73m^2
- The starting dose is 5mg once daily in the morning without regards to meals
- If additional glycemic control is needed, the dose may be increased to 10mg once daily in patients who have an eGFR of ≥ 60mL/min/1.73m^2.
- No dosage adjustment is needed for patients with mild renal impairment.
- Discontinue dapagliflozin if eGFR is persistently < 60mL/min/1.73m^2.
- No dosage adjustment is needed for patients with mild, moderate, or severe hepatic impairment. Dapagliflozin has not been studied in patients with severe hepatic impairment; therefore, the risk-benefit should be considered prior to use

Dosage form/strengths

Dapagliflozin is available as a5mg and 10mg film-coated tablet.

Efficacy

This review is limited to the approved doses dapagliflozin 5mg and 10mg. Included are 11 parent trials that are randomized, double-blind, controlled; 10 trials are 24 weeks duration and 1 is 52 weeks. There are 2 monotherapy trials, 2 add-on to metformin (1 is a comparator trial vs. glipizide), 2 initial combination with metformin XR, 1 add-on to glimepiride, 1 add-on to pioglitazone, 1 add-on to sitagliptin ± metformin, 1 add-on to insulin ± oral hypoglycemic agents, and 1 conducted in patients with preexisting cardiovascular disease (CVD) as add-on to their usual diabetes medications. Extension data have been published for 7 of the trials (add-on to: metformin, glimepiride pioglitazone, sitagliptin, and insulin trials) **Appendix 1**.

There are several ongoing or recently completed unpublished trials that include a trial in patients with renal impairment; cardiovascular disease and hypertension.

General **inclusion criteria** were type 2 diabetes, age ≥18 years, BMI≤45kg/m^2, C-peptide ≥ 1.0ng/ml. The A1C entry criteria for most studies were A1C 7.0-10%. General **exclusion criteria** were Scr ≥1.5mg/dL (males) ≥1.4mg/dL (females), urine albumin to creatinine ratio > 200 mg/mmol (or 1800mg/g), elevated liver function tests (e.g., ALT/AST >3x ULN), symptoms of severely uncontrolled hyperglycemia, significant renal, hepatic, hematological, oncological, endocrine, psychiatric or rheumatic disease, a cardiac vascular event within 6 months of study, congestive heart failure (NYHA 3 or 4), and severe uncontrolled BP (SBP ≥180, DBP ≥110). Exclusion criteria for the study in patients with preexisting CVD differed from above: CV event within 2 months of enrollment, NYHA class IV HF, unstable or acute CHF, systolic BP ≥160mmHg and/or diastolic BP ≥100mmHg.

For those studies that included combination with metformin, mean doses of metformin ranged between 1174-1950mg daily. For the comparator study by Nauck et al., the mean daily dose of dapagliflozin and glipizide was 9.2mg and 16.4mg respectively. For the insulin study by Wilding et al., the mean daily dose of insulin was 77.1 units (17% of patients were receiving basal only and the remainder basal/bolus). Fifty percent of the patients were also receiving an OHA (mostly metformin). In the sitagliptin trial by Jabbour et al., half the patients were on sitagliptin + metformin as the background medication and the other half were on sitagliptin alone. In the CVD study, 60% of patients were on insulin (mean dose 55 U/day) ± oral agent(s); those receiving insulin had their usual dose decreased by 25% at randomization with subsequent dose increases allowed.

Glycemic Efficacy **(Appendix 1)**

Average baseline A1C ranged between 7.7%-9.2%. The mean A1C for most studies was approximately 8.0%; patients enrolled in the add-on to pioglitazone and add-on to insulin and initial combination trials had higher baseline averages (A1C 8.3-9.2%). Rescue therapy with another anti-glycemic agent was allowed for most trials as defined by protocol.

Dapagliflozin significantly reduced A1C compared to placebo. For most trials, the mean reduction ranged from 0.63% to 0.89% for the 5mg dose and 0.82% to 0.97% for the 10mg dose compared to -0.13 to -0.4 with placebo. In the add-on to metformin active comparator trial, both dapagliflozin and glipizide reduced A1C by 0.5% at 52 weeks. In the initial combination therapy, the mean decrease in A1C with dapagliflozin + metformin XR was approximately 2.0% compared to 1.2-1.4% with dapagliflozin or metformin XR alone. In the preexisting CVD study, the addition of dapagliflozin 10mg decreased A1C by 0.3% compared to a 0.1% increase in the placebo group. This relatively lower response may have been because the dose of the patient's baseline insulin was reduced by 25% prior to adding on dapagliflozin or placebo (60% of patients were taking insulin).

Several studies evaluated change in A1C according to baseline A1C values. Similar to other agents used to treat diabetes, greater absolute reduction in A1C is seen in those with higher baseline values than those with lower baseline values. The preexisting CVD study evaluated efficacy according to those <65 and ≥ 65 years old and found no differences between groups.

Average baseline fasting plasma glucose (FPG) ranged between 156-185mg/dL. Dapagliflozin significantly reduced FPG relative to placebo. Mean reduction ranged from 18.7 to 29.6mg/dL and were fairly similar for both doses. For the initial combination therapy, the mean decrease in FPG with

dapagliflozin + metformin XR was approximately 60mg/dL compared to 34-46mg/dL with dapagliflozin or metformin XR alone.

Fewer patients in the dapagliflozin groups required rescue therapy compared to placebo. The extension trials indicate that glycemic efficacy is maintained beyond the initial 24 weeks.

Four studies evaluated 2-hour post-prandial glucose (2-h PPG) following an oral glucose tolerance test **Table 1**. For the 24-week trials, the mean decrease ranged from -32 to -67.5mg/dL with dapagliflozin versus +8.8 to -14.1mg/dL with placebo. There was very little difference in reduction in 2-h PPG between the 5mg and 10mg dose. Extension trial data showed that improvement in 2-h PPG is sustained over 48 weeks.

Table 1: Post-Prandial Glucose

2-hr PPG (mg/dL)	Monotherapy		Add-on to GLM			Add-on to PIO			Add-on to SIT±MET	
	DAP5	PBO	DAP5+ GLM4	DAP10+ GLM4	PBO+ GLM4	DAP5+ PIO≥30	DAP10+ PIO≥30	PBO+ PIO≥30	DAP10+ SIT100±MET	PBO+SIT100 ±MET
24 week	-51.7	8.8	-32	-34.9	-5.9	-65.1	-67.5	-14.1	-47.7	-4.8
48 week			-24.8**	-21.6**	N/A	-60.4	-80.9	-25.4	-43	-12.1

Abbreviations: DAP=dapagliflozin; GLM=glimepiride; MET=metformin; PBO=placebo; PIO=pioglitazone; SIT=sitagliptin
**Placebo-adjusted values

Weight **(Appendix 2)**
The urinary loss of glucose using SGLT2 inhibitors has been estimated to be 60-80g daily, which equates to approximately 200-300 kcal/day. Use of dapagliflozin monotherapy, or in combination with metformin or sitagliptin resulted in weight loss from baseline with means ranging from 2.1-3.6kg compared to 0.3-2.2kg with placebo. In the comparator trial, mean weight loss with dapagliflozin + metformin was 3.6kg versus a mean weight gain of 1.6kg with glipizide + metformin. In general, the magnitude of weight lost was less when dapagliflozin was combined with other agents known to cause weight gain (e.g., SUs, TZDs, insulin). More patients randomized to dapagliflozin had ≥5% decrease in weight.

Weight loss was maintained in the extension trials for the add-on to insulin, glimepiride and sitagliptin trials; however, the effect waned slightly in the add-on to metformin and pioglitazone trials.

Blood Pressure **(Appendix 2)**
There was a dose-dependent decrease in systolic blood pressure with dapagliflozin relative to placebo or active comparator. Mean changes with dapagliflozin across studies ranged from -0.8 to -6.7mmHg. Greater decreases were seen in the add-on to sitagliptin (5.4-6mmHg) and insulin (5.9-6.7mmHg) studies. Mean changes in diastolic blood pressure ranged from -1.0 to -3.1mmHg.

The product package insert warns of symptomatic hypotension that can occur after starting dapagliflozin particularly in those with impaired renal function, taking concomitant loop diuretics, and the elderly.

Safety
Particular emphasis has been placed on safety issues that were identified in preclinical or clinical trials from dapagliflozin or other SGLT2 inhibitors. Adverse events of interest with this class include urinary tract and genital infections, bone safety, photosensitivity, and events associated with decreased intravascular volume.

Approximately 80-96% of patients completed the trial with completion rates similar among both doses of dapagliflozin and placebo. The rate of AEs and discontinuations due to AEs for each trial are shown in **Appendix 3**.

Pooled data of adverse events occurring in at least 2% of patients are shown in **Table 2.** Urinary tract and genital mycotic infections are not shown in this table and are discussed separately.

Table2: Adverse Events Reported ≥2% of Patients

	DAP 5mg (n=1145)	DAP 10MG (n=1193)	Placebo (n=1193)
Nasopharyngitis	6.6	6.3	6.2
Back pain	3.1	4.2	3.2
Nausea	2.8	2.5	2.4
Influenza	2.7	2.3	2.3
Dyslipidemia	2.1	2.5	1.5
Constipation	2.2	1.9	1.5
Pain in extremity	2.0	1.7	1.4

Data obtained from product package insert

Hypoglycemia

Hypoglycemia was defined as blood glucose <63mg/dL regardless of presence of symptoms. Major hypoglycemia was defined as an episode requiring the assistance of another person due to severe impairment in consciousness or behavior with plasma glucose value <54mg/dL and prompt recovery after administration of glucose or glucagon.

The incidence of hypoglycemia is low when dapagliflozin is used as monotherapy or in combination with metformin, pioglitazone, or sitagliptin and is similar to placebo. The incidence of hypoglycemia is higher when combined with other drugs known to cause hypoglycemia such as SUs or insulin.

In the 52-week head-to-head trial of addition of dapagliflozin or glipizide to metformin the incidence of hypoglycemia was 3.4% and 39.7% respectively **(Appendix 3).** There were no cases of major hypoglycemia with dapagliflozin in any trial except for the combination with insulin trial (0.9-1.5% vs. 1.0% for DAP and placebo respectively) and 1 patient receiving triple oral therapy with DAP10+SIT±MET.

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 dapagliflozin compared to placebo/active comparators.

According to pooled results of 12 placebo-controlled trials, the rate of genital mycotic infection in females was 8.4%, 6.9%, and 1.5% for DAP5, DAP 10, and placebo respectively. In males, the rate was 2.8%, 2.75, and 0.3% respectively. Those with a prior history were more likely to have an infection during the trial than those with no prior history (23.1%, 25%, 10% versus 5.9%, 5%, 0.8% for DAP5, DAP10, and placebo respectively). The pooled rate of UTIs was 5.7%, 4.3%, and 3.7% respectively. Results according to individual trials are shown in **Appendix 3**.

Volume Depletion

Dapagliflozin can cause osmotic diuresis due to increased urinary glucose; therefore, adverse events related to volume depletion (dehydration, hypovolemia, orthostatic hypotension, hypotension) were evaluated. Patients with impaired renal function, those taking loop diuretics, and the elderly are at higher risk for these events (**Table 3**).

Table3: Reduced Intravascular Volume-Related Events

	Pool of 12 placebo-controlled trials			Pool of 13 placebo-controlled trials	
	DAP5 n/N (%)	DAP10 n/N (%)	Placebo n/N (%)	DAP10 n/N (%)	Placebo n/N (%)
Overall population	7/1145 (0.6)	9/1193 (0.8)	5/1393 (0.4)	27/2360 (1.1)	17/2295 (0.7)
Use of loop diuretics	0/40	3/31 (9.7)	1/55 (1.8)	6/236 (2.5)	4/267 (1.5)
eGFR ≥30 and <60mL/min/m^2	1/107 (0.9)	1/89 (1.1)	2/107 (1.9)	5/265 (1.9)	4/268 (1.5)
≥ 65 years old	1/216 (0.5)	3/204 (1.5)	1/276 (0.4)	11/665 (1.7)	6/711 (0.8)

Data obtained from product package insert

Renal Safety

The pooled results for change in serum creatinine (Scr) and eGFR for 12 placebo-controlled trials are shown in **Table 4**. Baseline Scr and eGFR was approximately 0.86mg/dL and 86ml/min/1.73m2 respectively. There was a small increase in mean Scr and decrease in mean eGFR in the dapagliflozin groups at week 1; values returned to baseline by week 24.

Results for a dedicated study in 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 changes in renal function compared to those in the pooled trials; the changes continued through weeks 24 and 52.

Table 4: Change in Serum Creatinine and Estimated GFR

	Pool of 12 placebo-controlled trials			Moderate renal impairment trial		
	DAP5 (n=1145)	DAP 10 (n=1193)	Placebo (n=1393)	DAP5 (n=83)	DAP 10 (n=85)	Placebo (n=84)
Week 1						
Serum creatinine (mg/dL)	0.029	0.041	-0.003	0.13	0.18	0.01
eGFR (ml/min/1.73m2)	-2.9	-4.1	0.4	-3.8	-5.5	0.5
Week 24						
Serum creatinine (mg/dL)	-0.001	0.001	-0.005	0.08	0.16	0.02
eGFR (ml/min/1.73m2)	0.8	0.3	0.8	-4.0	-7.4	0.03
Week 24						
Serum creatinine (mg/dL)	-	-	-	0.06	0.15	0.10
eGFR (ml/min/1.73m2)				-4.2	-7.3	-2.6

Data obtained from product package insert

Renal impairment-related AEs occurred at a greater frequency in patients ≥65 years old and moderate renal impairment (eGFR ≥30 and < 60ml/min/1.73m2) **Table 5**. The labeling for dapagliflozin states that it should not be initiated in patients with eGFR < 60mL/min/1.73m^2.

Table 5: Patients with ≥1 Renal Impairment-Related Adverse Reaction

	Pool of 6 placebo-controlled trials			Pool of 9 placebo-controlled trials	
	DAP5 n/N (%)	DAP10 n/N (%)	Placebo n/N (%)	DAP10 n/N (%)	Placebo n/N (%)
Overall population	14/767 (1.8)	16/859 (1.9)	13/785 (1.7)	136/2026 (6.7)	82/1956 (4.2)
≥65 years old	5/162 (3.1)	6/159 (3.8)	4/190 (2.1)	87/620 (14)	52/655 (7.9)
eGFR ≥30 and < 60ml/min/1.73m2	7/88 (8.0)	9/75 (12)	5/77 (6.5)	71/251 (28.3)	40/249 (16.1)
≥65 years old and eGFR ≥30 and < 60ml/min/1.73m2	3/43 (7.0)	4/35 (11.4)	2/41 (4.9)	47/134 (35.1)	27/141 (19.1)

Data obtained from product package insert (includes information from long-term extension trials)

Effect on lipids

According to pooled data from 13 placebo-controlled trials, the mean percent change in total cholesterol for dapagliflozin was 2.5% versus 0.0% for placebo; the change in LDL cholesterol was 2.9% and -1.0% for dapagliflozin and placebo respectively. Results for individual trials, where available, are shown in **Table 6**. The individual trials show that HDL-C is increased and triglycerides decreased with dapagliflozin relative to placebo.

Table 6: Percent Change in Cholesterol and Triglycerides

		24 weeks				48 weeks*			
Study		**TC**	**LDL-C**	**HDL-C**	**TG**	**TC**	**LDL-C**	**HDL-C**	**TG**
Bailey 2012	DAP5	2.0	1.9	9.7	-5.9	-	-	-	-
	PBO	3.8	3.7	10.5	-5.2				
Bailey 2010	DAP5 + MET	2.2	3.1	3.3	-6.2	-	-	-	-
	DAP10 + MET	4.2	9.5	4.4	-6.2				
	PBO + MET	2.7	3.5	0.4	2.1				
Nauck 2011	DAP + MET	-	-	-	-	1.5	-0.5	5.9	-1.1
	GPZ + MET					-0.6	-0.9	-0.2	-0.8
Strojek 2011/2014	DAP5+GLIM4	1.8	0.9	4.5	-4.0	2.2	5.7	7.9	-0.9
	DAP10+GLIM4	0.7	2.3	5.2	-10.6	1.5	3.9	10.4	-3.7
	PBO+GLIM4	1.1	0.8	2.4	0.3	-0.5	-0.6	5.5	3.1
Rosenstock 2012	DAP5/10+PIO ≥30	-	-	-	-	0-2.0	1.1-3.4	4.1-7.2	3.7-4.2
	PBO+ PIO ≥30					1.9	4.5	1.3	13.5
Jabbour 2014	DAP10 + SIT±MET	3.2	2.4	7.4	-2.1	2.1	0.1	9.7	-2.8
	PBO+ SIT±MET	-0.6	-1.9	1.7	0.1	0.3	-2.4	3.7	2.1

*Results for Nauck are at 52 weeks

^Unadjusted values are shown for the 48 week data for Strojek

Cardiovascular Safety

Under FDA requirements, a meta- analysis of MACE is to be conducted for new diabetes drugs submitted for approval. The FDA recommends that point estimates and 95% confidence intervals (CI) be calculated comparing the incidence of events with the investigational drug to that occurring in the control group and that the upper bound of the 95% CI is < 1.8.

The primary endpoint (MACE-plus) was the composite of cardiovascular (CV) death, myocardial infarction (MI), and stroke and hospitalization for unstable angina. Endpoints for MACE included CV death, MI, and stroke.

The pooled data include 21 Phase 2b and Phase 3 trials. Two of the 21 trials were conducted in patients with pre-existing CVD. Pooled data are presented for the 21 trials, a separate analysis for the 2 pre-existing CVD trials, and a separate analysis for patients with a prior history of CV disease in from the general clinical trials (excluding the 2 trials specifically designed in a CVD population)

The pooled results for the 21 trials show no increased risk for CV events with dapagliflozin. For the pooled analysis of trials 18 and 19 some of the HR and upper bound of 95% CI exceeded 1.0 and 1.8 respectively which raises the question of whether dapagliflozin poses an increased CV risk in these patients. For patients with a history of CV disease, excluding the preexisting CVD trials , the MACE-plus and MACE analyses did not show increased risk with dapagliflozin; however, some of the component items had an HR that either exceeded 1.0 or a upper bound of the 95% CI that exceeded 1.8 (**Table 7**).

Table 7: Cardiovascular Events

	Pooled 21 trials (including preexisting CVD trials) Events/Rate per 1000PY			Pooled preexisting CVD trials Events/Rate per 1000PY			Patients with history of CV disease (excluding preexisting CVD trials) Events/Rate per 1000PY		
	DAP N=5936 PY=6594	COMP N=3403 PY =3831	HR [95%CI]	DAP N=942 PY=1118	COMP N=945 PY =1119	HR [95%CI]	DAP N=919 PY=1166	COMP N=417 PY =510	HR [95%CI]
MACE-plus*	97/14.7	81/21.1	0.81 [0.59, 1.09]	43/38.5	44/39.3	0.98 [0.64, 1.49]	25/21.4	17/33.3	0.53 [9.28, 1.02]
MACE**	73/11.1	62/16.2	0.78 [0.55, 1.11]	32/28.6	29/25.9	1.11 [0.67, 1.83]	18	16	0.41 [0.20, 0.84]
CV death	20	18	0.71 [0.35, 0.97]	8	9	0.89 [0.34, 2.3]	8	4	0.65 [0.19, 2.22]
MI	31	33	0.59 [0.35, 0.97]	12	12	1.00 [0.45, 2.23]	6	10	0.24 [0.08, 0.68]
Stroke	25	18	1.00 [0.54, 1.86]	12	10	1.21 [0.52, 2.8]	6	4	0.62 [0.16, 2.37]
Hosp. for unstable angina	27	20	0.91 [0.50, 1.66]	12	15	0.80 [0.37, 1.7]	7	1	2.52 [0.30, 21.33]

Data obtained from FDA Advisory Committee briefing documents
*Primary composite endpoint (CV death, MI, stroke, hospitalization for unstable angina)
**MACE (CV death, MI, stroke)

A large randomized, placebo-controlled, long-term cardiovascular safety trial is underway in patients who are at risk for CV disease. Patients will be randomized to receive dapagliflozin 10mg or placebo in addition to their background medications. Planned enrollment will be approximately 22,000 patients with follow-up for up to 6 years. The primary CV endpoint is a composite of CV death, MI, and ischemic stroke. Estimated study completion date is April 2019.

Bone Safety

In pre-clinical trials using rats, hyperostosis (increased trabecular bone content) was seen. Because of this and that the SGLT2 inhibitors may also alter renal tubule reabsorption of calcium and phosphate, vitamin D metabolism, and result in weight loss, the safety of dapagliflozin on bone was examined.

In the pooled 24-week placebo-controlled trials, the changes in serum calcium, parathyroid hormone, vitamin D were small and of uncertain clinical relevance. There was an increase in mean magnesium concentration with DAP10mg compared to placebo (0.09mEq/L vs. -0.02mEq/L).

Markers of bone turnover and bone formation, bone mineral density (BMD), and other biochemical measurement relevant to bone metabolism were evaluated in a 50 week study. Women 55-75 years old that were post-menopausal for ≥ 5 years and men 30-75 years old were randomized to addition of dapagliflozin 10mg (n=89) or placebo (n=91) to ongoing metformin. Patients were excluded if they had BMD T-scores < -2.0 at lumbar spine, femoral neck or total hip at baseline or receiving treatments known to significantly influence bone metabolism (e.g., bisphosphonates, calcitonin, corticosteroids, hormone replacement therapy). Patients taking vitamin D and/or calcium supplementation were allowed to continue them and were instructed not to change the dose.

Serum C-terminal cross-linking telopeptides of type I collagen (CTX) was used to assess bone resorption and procollagen type 1 N-terminal propeptide (P1NP) for bone formation. There were no significant effects on these markers with dapagliflozin or placebo.

Bone mineral density as measured by DXA showed no significant difference in percent change from baseline between dapagliflozin and placebo for the 3 measured regions (lumbar spine, femoral neck, and total hip). The proportion of patients who had ≥ 3% decrease in BMD from baseline was also assessed. Slightly higher percentage of patients in the dapagliflozin had ≥3% decrease from baseline than placebo; however, the difference was not significant. The difference from placebo was 3.8% (lumbar spine), 2.5% (femoral neck), and 3.3% (total hip). There were no significant gender-based differences. Data out to

102-weeks showed the mean placebo-subtracted difference from baseline for BMD at the lumbar spine, femoral neck and total hip were 0.22 (-0.89, 1.34), -0.94 (95% CI, -2.21, 0.35) and -0.45 (-1.32, 0.43), respectively.

A 104-week trial conducted in patients with moderate renal impairment found an imbalance in fracture events with the groups receiving dapagliflozin; 5 patients (DAP5), 8 patients (DAP10), and none receiving placebo). As discussed earlier, dapagliflozin should not be used in patients with an eGFR <60 mL/min/1.73 m^2.

In the overall pooled dataset, there was not an increased fracture rate with dapagliflozin. The fracture rate was 23/2026 (1.1%) and 32/1956 (1.6%) for the dapagliflozin and placebo groups respectively.

Malignancies
A potential safety signal for breast and bladder cancer was identified with dapagliflozin. This finding was unexpected because breast and bladder tissue do not express the SGLT2 transporter nor did 2-year carcinogenic studies in animals show any pre-neoplastic or neoplastic activity. Also, exposure to dapagliflozin was generally < 1 year and these cancers can take years to develop.

Based on 22 clinical trials, newly diagnosed cases of bladder cancer were reported in 10/6045 (0.17%) of patients receiving dapagliflozin compared to 1/3512 (0.03%) of patients receiving comparator/placebo. After excluding patients who were exposed to study less than 1 year, there were 4 cases of bladder cancer with dapagliflozin and no cases with comparator/placebo. There were too few cases of bladder cancer to determine whether these events are related to dapagliflozin. **See Warnings and Precautions**

In the pooled data, there were 12 cases of breast cancer reported among 2693(0.45%) females treated with dapagliflozin compared to 3 out of 1439 (0.21%) females treated with placebo. Three additional cases were later reported in patients receiving dapagliflozin (1 was from an open-label study with no placebo control). For the 12 cases reported with the controlled trials, the time to diagnosis of breast cancer was 6 to 722 days; 13 out of 15 cases were diagnosed within one year of exposure to study drug. Nine of the 12 cases in the dapagliflozin arms were estrogen receptor positive which is suggestive of relatively slow-growing tumors). The FDA reviewer felt that the risk of breast cancer with dapagliflozin was inconclusive.

Carcinogenicity studies in rodents were not associated with increased cancer risk.

Hypersensitivity
Across the clinical program, serious anaphylactic reactions and severe cutaneous reactions were reported in 0.3% and 0.2% of dapagliflozin- and comparator-treated patients. Discontinue dapagliflozin if hypersensitivity reactions occur and treat per standard of care.

Look-alike / Sound-alike (LASA) Error Risk Potential

As part of a Joint Commission standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

Table 8: Results of LASA Search

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Dapagliflozin	None	None	None**	Canagliflozin Empagliflozin
Farxiga	None	None	None	Zytiga

**High Alert Medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Contraindications

- History of a serious hypersensitivity reaction to dapagliflozin
- Severe renal impairment, end stage renal disease, or patients on dialysis

Warnings and Precautions

Hypotension: Dapagliflozin causes intravascular volume contraction. Symptomatic hypotension may occur after initiation of dapagliflozin particularly in patients with eGFR <60mL/min/1.73m^2, elderly patients, those taking loop diuretics Volume status should be assessed and corrected before initiating dapagliflozin in patients with these characteristics. Monitor for signs and symptoms after initiating therapy.

Impairment in renal function: Dapagliflozin increases serum creatinine and decreases eGFR. Elderly patients and patients with impaired renal function may be more susceptible to these changes. Evaluate renal function prior to initiating dapagliflozin and periodically thereafter.

Hypoglycemia with concomitant use with insulin or insulin secretagogues: The risk of hypoglycemia can be increased when dapagliflozin 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: Dapagliflozin increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections.

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

Bladder cancer: Based on 22 clinical trials, newly diagnosed cases of bladder cancer were reported in 10/6045 (0.17%) of patients receiving dapagliflozin compared to 1/3512 (0.03%) of patients receiving comparator/placebo. After excluding patients who were exposed to study less than 1 year, there were 4 cases of bladder cancer with dapagliflozin and no cases with comparator/placebo. There were too few cases of bladder cancer to determine whether these events are related to dapagliflozin.

There are insufficient data to determine if dapagliflozin has an effect on pre-existing bladder tumors. Dapagliflozin should not be used in patients with active bladder cancer. In those with a prior history of bladder cancer, the product labeling states that risk versus benefit be considered.

Increase in Hematocrit: Pooled data from 13 placebo-controlled trials showed that at week 24, the mean change in hematocrit was 2.3% in the dapagliflozin group and -0.33% in the placebo group. More patients in the dapagliflozin groups had a hematocrit >55% (1.3% and 0.4% in the dapagliflozin 10mg and placebo groups respectively).

Drug Interactions

No meaningful drug interactions were noted (see product package insert).

Pregnancy and Nursing

Pregnancy Category C: In rat studies, dapagliflozin may effect renal development and maturation. The timing of these effects corresponds to 2nd and 3rd trimester of human development; therefore consider alternate therapy during pregnancy especially during the 2nd and 3rd trimester.

Dapagliflozin is secreted in milk of lactating rats. It is not known if dapagliflozin is excreted in human milk. Data in juvenile rats showed risk to the developing kidney during maturation. In humans, kidney maturation occurs *in utero* and in the first 2 years of life. Because of the potential for serious adverse reactions to the nursing infant, a decision should be made to discontinue dapagliflozin or nursing taking into account the importance of the drug to the mother.

Conclusions

Dapagliflozin is the second SGLT2 inhibitor available in the US. Average change in A1C is ≤ 1.0%.

Based on the clinical trial data, increasing the dose of dapagliflozin from 5mg to 10mg does not appear to offer additional meaningful efficacy. In the only head-to-head active comparator trial, the efficacy of dapagliflozin was found to be similar to glipizide. Trials directly comparing dapagliflozin to other oral third line agents such as pioglitazone and the DPP-4 inhibitors are needed.

Advantages of dapagliflozin include low risk of hypoglycemia and weight loss. Adverse reactions most likely attributed to dapagliflozin mechanism of action include increased incidence of genital mycotic infections, UTIs, osmotic diuresis and reduced intravascular volume related events.

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Contact person: Deb Khachikian, Pharm.D., Pharmacy Benefits Management Services

Appendix 1: Glycemic Efficacy (Primary and Extension Trials)

Study	Duration	Patients	Treatment arms	n	Baseline A1C (%)	A1C (%)	A1C < 7% (%)	Baseline FPG (mg/dL)	FPG (mg/dL)	Rescue drug	Rescue* (%)
Bailey 2012	24 weeks	Treatment naive	DAP5 PBO	68 68	7.9 7.8	-0.82 0.02	48.5 38.2	157.0 161.4	-28.4 4.1	MET	5.9 19.1
Ferrannini 2010	24 weeks	Treatment naive	DAP5 DAP10 PBO	64 70 75	7.86 8.01 7.84	-0.77 -0.89 -0.23	44 51 32	162.2 166.6 159.9	-24.1 -28.8 -4.1	MET	Not shown
Bailey 2010	24 weeks	Inadequate control on MET	DAP5 + MET DAP10 + MET PBO + MET	137 135 137	8.17 7.92 8.11	-0.70 -0.84 -0.30	38 41 26	169.0 155.9 165.4	-21.4 -23.4 -5.9	PIO or ACARB	See 102 wk results
Nauck 2011	52 weeks	Inadequate control on MET±1 OAD	DAP + MET GPZ + MET	406 408	7.7 7.7	-0.5 -0.5	27.4 32.0	162.0 163.8	-22.3 -18.7	No	N/A
Strojek 2011	24 weeks	Inadequate control on SU	DAP5+GLM4 DAP10+GLM4 PBO+GLM4	142 151 145	8.12 8.07 8.15	-0.63 -0.82 -0.13	30.3 31.7 13.0	174.2 171.9 172.4	-21.2 -28.4 -2.0	MET or PIO	5.6 2.0 16.2
Henry 2012	24 weeks	Initial combination	DAP5+MET XR DAP5 MET XR	194 203 201	9.2 9.1 9.2	-2.05 -1.19 -1.35	52.4 22.5 34.6	193.7 190.6 196.9	-61.0 -41.9 -33.5	PIO or SIT or ACARB	0.5 7.4 12.9
Henry 2012	24 weeks	Initial combination	DAP10+MET XR DAP10 MET XR	211 219 208	9.1 9.1 9.1	-1.98 -1.45 -1.44	46.6 31.7 35.2	189.4 197.8 190.3	-60.3 -46.4 -34.7	PIO or SIT or ACARB	1.4 7.8 13.5
Rosenstock 2012	24weeks	Inadequate control on PIO	DAP5+PIO ≥30 DAP10+PIO ≥30 PBO+ PIO ≥30	141 140 139	8.40 8.37 8.34	-0.82 -0.97 -0.42	- - -	168.6 164.9 160.7	-24.9 -29.6 -5.5	MET or SU	11-18 (5+10mg) 34
Wilding 2012	24 weeks	Insulin ±OAD	DAP5 + INS ±OAD DAP10+ INS ±OAD PBO + INS ±OAD	211 194 193	8.62 8.57 8.47	-0.89 -0.96 -0.39	- - -	185.4 173.1 170.6	-20.2 -19.8 -	No	N/A
Jabbour 2014	24 weeks	Inadequate control on MET, DPP4I, or both	DAP10 + SIT100±MET PBO+ SIT100±MET	225 226	7.9 8.0	-0.5 0.0	27.8 17.9	162.2 163.0	-24.1 3.8	GLM	See 48 wk results
Leiter 2014	24 weeks	Preexisting CVD Inadequate control on AHA	DAP10+AHA PBO+ AHA	480 482	8.0 8.1	-0.3 0.1	18.7 12.6	161.9 166.2	-14.0 10.9	OHA or insulin	7.5 22.6
Bailey 2013	Extension (total 102 wks)	Inadequate control on MET	DAP5 + MET DAP10 + MET PBO + MET	122 119 115	8.17 7.92 8.12	-0.58 -0.78 0.02	26.4 31.5 15.4	169 156 165	-26.5 -24.5 -10.4	PIO or ACARB	46.0 42.2 60.6
Nauck 2014	Extension (total 104 wks)	Inadequate control on MET±1 OAD	DAP + MET GPZ + MET	406 408	7.50 7.56	-0.32 -0.14	- -	162.0 163.8	-20.2 -12.2	No	N/A
Strojek 2014	Extension (total 48 weeks)	Inadequate control on SU	DAP5+GLM4 DAP10+GLM4 PBO+GLM4	142 151 145	8.12 8.07 8.15	-0.82 -0.98 -0.48	28.2 30.5 10.3	174.2 171.9 172.4	-16.6 -28.8 2.52	MET or PIO	29.6 17.9 53.1
Rosenstock 2012	Extension (total 48 weeks)	Inadequate control on PIO	DAP5+PIO ≥30 DAP10+PIO≥30 PBO+ PIO≥30	122 125 115	8.40 8.37 8.34	-0.95 -1.21 -0.54	- - -	168.6 164.9 160.7	-22.8 -33.1 -13.1	MET or SU	- - -
Wilding 2012	Extension (total 48 weeks)	Insulin ±OAD	DAP5 + INS ±OAD DAP10+ INS ±OAD PBO + INS ±OAD	211 194 193		-0.96 -1.01 -0.47			-16.2 -16.9 -	No	N/A
Jabbour 2014	Extension (total 48 weeks)	Inadequate control on MET, DPP4I, or both	DAP10 + SIT100±MET PBO+ SIT100±MET	208 202	7.9 8.0	-0.3 0.4	22.1 12.0	162.2 163.0	-19.7 13.5	GLM	31.8 57.6
Leiter 2014	Extension (total 52 weeks)	Preexisting CVD Inadequate control on AHAs	DAP10+AHA PBO+ AHA	480 482	8.0 8.1	-0.5 0.0	18.8 9.9	161.6 165.6	-16.4 2.7	OHA or insulin	18.7 43.6

Abbreviations: ACARB=acarbose; AHA=anti-hyperglycemic agents; CVD=cardiovascular disease; DAP=dapagliflozin; pressure; DPP4I=dipeptidyl-peptidase 4 inhibitor; FPG=fasting plasma glucose; GLM=glimepiride; GPZ=glipizide; INS=insulin; MET=metformin; OAD=oral antidiabetic drug; PBO=placebo; PIO=pioglitazone; SIT=sitagliptin; SU=sulfonylurea

**received rescue drug or discontinued for not achieving glycemic goal

Appendix 2: Weight and Blood Pressure (Primary and Extension Trials)

Study	Duration	Patients	Treatment arms	n	Baseline weight (kg)	Weight (kg)	≥5% ↓ in wt. (%)	SBP/DBP (mmHg)
Bailey 2012	24 weeks	Treatment naive	DAP5	68	85.4	-2.7	34.3	-4.6
			PBO	68	90.0	-1.0	7.4	0.8
Ferrannini 2010^	24 weeks	Treatment naive	DAP5	64	87.6	-2.8		-2.3/-1.7
			DAP10	70	94.2	-3.2		-3.6/-2.0
			PBO	75	88.8	-2.2		-0.9/-0.7
Bailey 2010^	24 weeks	Inadequate control on MET	DAP5 + MET	137	84.7	-3.0	19.5	-4.3/-2.5
			DAP10 + MET	135	86.3	-2.9	22.1	-5.1/-1.8
			PBO + MET	137	87.7	-0.9	?	-0.2/-0.1
Nauck 2011^	52 weeks	Inadequate control on MET±1 OAD	DAP + MET	406	96.4	-3.6		-4.3/-1.6
			GPZ + MET	408	96.5	1.55		0.8/-0.4
Strojek 2011^	24 weeks	Inadequate control on SU	DAP5+GLM4	142	81.0	-1.6		-4.0/-1.7
			DAP10+GLM4	151	80.6	-2.3		-5.0/-2.8
			PBO+GLM4	145	80.9	-0.7		-1.2/-1.4
Henry 2012	24 weeks	Initial combination	DAP5+MET XR	194	84.1	-2.7		-2.9/-2.2
			DAP5	203	86.2	-2.6		-4.2/-3.0
			MET XR	201	84.6	-1.3		-1.8/-0.4
Henry 2012	24 weeks	Initial combination	DAP10+MET XR	211	88.4	-3.3		-3.3/-1.8
			DAP10	219	88.5	-2.7		-4.0/-1.9
			MET XR	208	87.2	-1.4		-1.2/0.0
Rosenstock 2012^	24weeks	Inadequate control on PIO	DAP5+PIO ≥30	141	87.8	0.1		-0.8/-1.0
			DAP10+PIO ≥30	140	84.8	-0.1		-3.4/-3.1
			PBO+ PIO ≥30	139	86.4	1.6		1.3/0.7
Wilding 2012	24 weeks	Insulin ±OAD	DAP5 + INS ±OAD	211	93.3	-1.0		-5.9/-3.0
			DAP10+ INS ±OAD	194	94.5	-1.6		-6.7/-2.7
			PBO + INS ±OAD	193	94.5	0.4		-3.6/-1.9
Jabbour 2014^	24 weeks	Inadequate control on MET, DPP4I, or both	DAP10 + SIT100±MET	225	91.0	-2.1		-6.0/-
			PBO+ SIT100±MET	226	89.2	-0.3		-5.1/-
Leiter 2014^	24 weeks	Preexisting CVD Inadequate control on AHAs	DAP10+AHA	480	94.5	-2.5	22.0	-2.7/-
			PBO+ AHA	482	93.2	-0.6	9.1	0.3/-
Bailey 2014	Extension (total 102 wks)	Inadequate control on MET	DAP5 + MET	122	84.7	-1.7		-1.1/-1.5
			DAP10 + MET	119	86.3	-1.7		-0.3/-1.2
			PBO + MET	115	87.7	1.4		1.5/-1.0
Nauck 2014	Extension (total 104 wks)	Inadequate control on MET±1 OAD	DAP + MET	406	96.4	-3.7	23.8	-2.7/-
			GPZ + MET	408	96.5	1.4	2.8	1.2/-
Strojek 2014	Extension (total 48 weeks)	Inadequate control on SU	DAP5+GLM4	142	81.0	-1.54		-3.0/-1.4
			DAP10+GLM4	151	80.6	-2.41		-4.2/-2.1
			PBO+GLM4	145	80.9	-0.77		1.8/0.79
Rosenstock 2012	Extension (total 48 weeks)	Inadequate control on PIO	DAP5+PIO	122	87.8	1.35		-1.0/-0.7
			DAP10+PIO	125	84.8	0.69		-2.2/-2.4
			PBO+ PIO	115	86.4	2.99		2.0/0.4
Wilding 2012	Extension (total 48 weeks)	Insulin ±OAD	DAP5 + INS ±OAD	211		-1.0		-4.3/-2.6
			DAP10+ INS ±OAD	194		-1.6		-4.1/-2.9
			PBO + INS ±OAD	193		0.82		-1.5/-1.3
Jabbour 2014	Extension (total 48 weeks)	Inadequate control on MET, DPP4I, or both	DAP10 + SIT100±MET	208	91.0	-2.2		-5.4/-
			PBO+ SIT100±MET	202	89.2	-0.2		-5.2/-
Leiter 2014	Extension (total 52 weeks)	Preexisting CVD Inadequate control on AHA	DAP10+AHA	480	94.5	-3.2		-3.6/-
			PBO+ AHA	482	93.2	-1.1		-0.9/-

Abbreviations: AHA=antiglycemic agents; CVD=cardiovascular disease; DAP=dapagliflozin; DBP=diastolic blood pressure; DPP4I=dipeptidyl-peptidase 4 inhibitor; GLM=glimepiride; GPZ=glipizide; INS=insulin; MET=metformin; OAD=oral antidiabetic drug; PBO=placebo; PIO=pioglitazone; SBP=systolic blood pressure; SIT=sitagliptin; SU=sulfonylurea

Appendix 3: Selected Safety Information (Values shown as percent unless otherwise indicated)

Study	Duration	Treatment arms	n	≥ 1 AE	≥ 1 Tx related AE	d/c due to AE	≥ 1SAE	Deaths (n)	Overall hypoglycemia	Major Hypoglycemia	UTI Male/female	Genital infection Male/female	Hypotensive Events
Bailey 2012	24 weeks	DAP5	68	57.4	7.4	0	0	0	1.5	0	3.1/2.8	0.0/5.6	1.5
		PBO	68	60.3	11.8	0	0	0	0	0	2.7/0.0	2.7/3.2	0
Ferrannini 2010	24 weeks	DAP5	64	57.8	-	4.7	1.6	0	0	0	12.5	7.8	0
		DAP10	70	68.6	-	7.1	1.4	1	2.9	0	5.7	12.9	1.4
		PBO	75	60.0	-	1.3	4.0	0	2.7	0	4.0	1.3	1.3
Bailey 2010	24 weeks	DAP5 + MET	137	69	18	2	3	0	4	0	7	13	1.0
		DAP10 + MET	135	73	23	3	3	0	4	0	8	9	0
		PBO + MET	137	64	16	4	4	0	3	0	8	5	<1
Nauck 2011	52 weeks	DAP + MET	406	78.3	27.1	9.1	8.6	0	3.4	0	10.8/14.4	5.3/21.1	1.5
		GPZ + MET	408	77.9	27.0	5.9	11.3	3	39.7	0.7	6.4/9.2	0.4/5.4	0.7
Strojek 2011	24 weeks	DAP5+GLM4	142	48.3	7.6	3.4	6.9	0	6.9	0	5.6/8.2	2.8/9.6	0
		DAP10+GLM4	151	50.3	9.3	2.6	6.0	1	7.9	0	3.0/7.1	6.1/7.1	0.7
		PBO+GLM4	145	47.3	3.4	2.1	4.8	0	4.8	0	0/12	0/1.3	0
Henry 2012	24 weeks	DAP5+MET XR	194	68.6	19.1	1.0	3.1	0	2.6	0	2.6/11.2	5.1/7.8	0.5
		DAP5	203	52.7	14.3	2.5	4.4	1	0	0	4.3/10.8	1.1/11.7	2.0
		MET XR	201	59.2	14.9	3.0	3.5	0	0	0	3.2/11.3	0/3.8	0
Henry 2012	24 weeks	DAP10+MET XR	211	59.7	16.1	1.9	1.4	0	3.3	0	5.7/9.5	5.7/11.4	0
		DAP10	219	60.3	21.5	4.1	2.3	0	0.9	0	5.7/15.8	6.7/18.4	0.9
		MET XR	208	56.7	15.4	3.8	1.9	1	2.9	0	3.1/5.4	2.1/2.7	0
Jabbour 2014	24 weeks	DAP10 + SIT100±MET	225	52.9	-	3.1	4.4	See 48 wk results	2.7	0	4.9	8.4	See 48 wk results
		PBO+ SIT100±MET	226	48.2	-	2.2	4.0		1.0	0	4.0	0.4	
Bailey 2013 Extension	102 weeks total	DAP5 + MET	137	81.0	24.1	3.6	6.6	0	5.1	0	2.9/14.7	5.8/23.5	2.2
		DAP10 + MET	135	82.2	33.3	4.4	10.4	0	5.2	0	5.2/24.1	6.5/20.7	1.5
		PBO + MET	137	81.0	20.4	6.6	10.2	1	5.8	0	3.9/13.1	0/11.5	1.5
Nauck 2014 Extension	104 weeks total	DAP + MET	406	83.0	30.0	9.9	12.6	0	4.2	0	10.2/17.8	8.0/23.3	1.5
		GPZ + MET	408	82.8	28.9	7.6	15.2	4	45.8	0.7	4.9/14.1	0.4/5.9	1.7
Strojek 2014 Extension	48 weeks total	DAP5+GLM4	142	60.7	8.3	3.4	11.0	0	10.3	0	5.6/9.6	2.8/9.6	0
		DAP10+GLM4	151	58.9	10.6	2.6	8.6	1	11.3	0	6.1/9.4	7.6/9.4	0.7
		PBO+GLM4	145	55.5	5.5	3.4	8.9	0	6.8	0	1.4/13.3	0/2.7	0
Rosenstock 2012 Extension	48 weeks total	DAP5+PIO ≥30	122	68.1	-	3.5	4.3	1	2.1	0	8.5	9.2	0
		DAP10+PIO ≥30	125	70.7	-	2.1	1.4	0	0	0	5.0	8.6	0
		PBO+ PIO≥30	115	66.9	-	3.6	2.9	0	0.7	0	7.9	2.9	0
Wilding 2012 Extension	48 weeks total	DAP5 + INS ±OAD	212	72.2	29.2	7.1	9.0	2	55.7	0.9	5.0/16.1	2.0/17.0	2.4
		DAP10+ INS ±OAD	196	74.0	29.1	5.1	11.7	0	53.6	1.5	5.7/13.9	9.1/12.0	1.5
		PBO + INS ±OAD	197	73.1	20.8	4.6	13.2	0	51.8	1.0	3.1/7.1	0.0/5.1	1.0
Jabbour 2014 Extension	48 weeks total	DAP10 + SIT100±MET	225	66.2	-	3.1	6.7	0	5.3	N=1	6.7	9.8	N=3
		PBO+ SIT100±MET	226	61.1	-	3.1	8.0	1	6.2	0	6.2	0.4	N=2

Leiter 2014 Extension‡	52 weeks total	DAP10+AHA	480	73.9	22.0	9.3	16.2	5	28.2	0	7.1/18.9	5.9/10.7	1.5
		PBO+ AHA	482	68.7	12.0	8.1	18.4	4	25.3	0	2.5/12.5	0.3/0.6	2.7

Abbreviations: AE=adverse event; DAP=dapagliflozin; GLM=glimepiride; GPZ=glipizide; INS=insulin; MET=metformin; OAD=oral antidiabetic drug; PBO=placebo; PIO=pioglitazone; SAE=serious adverse event; SIT=sitagliptin; UTI=urinary tract infection

‡60% of patients were on concomitant insulin