Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

New Drug Evaluation: Canagliflozin and Metformin

Month/Year of Review: January 2015
Generic Name: Canagliflozin and Metformin
PDL Class: Oral Hypoglycemics

End date of literature search: November 17, 2014
Brand Name (Manufacturer): Invokamet ™ (Janssen Pharmaceuticals)
Dossier Received: Yes

FDA Approved Indication:[1]
Canagliflozin/metformin (CM) fixed combination product is a sodium-glucose co-transporter 2 (SGLT2) inhibitor and biguanide combination for use as an adjunct to diet and exercise to improve glucose levels in patients with type 2 diabetes (T2DM) who are not adequately controlled on a regimen containing metformin or canagliflozin or in patients already being treated with both canagliflozin and metformin.

Research Questions:
- Is there evidence of superior efficacy of CM compared to other T2DM therapies when considering important outcomes such microvascular outcomes, macrovascular outcomes and long term hemoglobin A1c (HbA1c) goal attainment?
- Is there evidence CM has a better safety profile than other treatments for T2DM?
- Are there subgroups of patients, which CM shows improved efficacy, or greater risk of harms?

Conclusions:
- There is insufficient evidence at this time that CM reduces microvascular outcomes, macrovascular outcomes or mortality.
- FDA approval of the CM fixed combination product was based on the Agency's previous findings on safety and efficacy of canagliflozin single product approved March 2013, and metformin hydrochloride single product approved in 1995. Canagliflozin was originally reviewed by this P&T Committee in September 2013 the oral hypoglycemic class was last reviewed by this P&T Committee in September 2014.
- There is insufficient evidence at this time that adding canagliflozin to metformin further reduces microvascular or macrovascular outcomes.
- There is moderate strength of evidence that adding canagliflozin to patients already on metformin (± other background therapy) lowers HbA1c by -0.55% to -1.06% in published studies lasting 26-52 weeks.[2-7] Fair to good quality trials show that 300 mg of canagliflozin combined with metformin were superior to sitagliptin and glimepiride monotherapy. Canagliflozin 100 mg in combination with metformin was non-inferior to sitagliptin and glimepiride.
- The most common adverse effects seen with adding canagliflozin to metformin are female genital mycotic infections, urinary tract infections and increased urination. In published studies, withdrawals due to adverse reactions ranged from 1.8% to 9.5%.[1-7]
- Adding canagliflozin to metformin is unlikely to cause hypoglycemia and has demonstrated positive effects on blood pressure (BP), high-density lipoprotein (HDL) and body weight while causing a dose-related increase in low-density lipoprotein (LDL) levels; long term clinical significance of these effects are

unknown.[1] Hypotension has been associated with canagliflozin and hypovolemia should be corrected prior to initiation. Patients at increased risk are those patients with renal impairment, elderly patients, patients with low systolic blood pressure, or on angiotensin-converting-enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB).[1]

- Canagliflozin is currently recommended as a fourth line agent (Appendix 1).

Recommendations:

- Add the CM fixed combination product to the current prior authorization criteria for SGLT2 inhibitors (Appendix 1) and limit the use of CM to patients that have tried and failed other treatments for T2DM. No changes to the PDL are recommended.

Reason for Review:

CM is a fixed combination product used for controlling elevated glucoses in patients with T2DM. Comparison of the efficacy and safety data of CM to other T2DM treatments is necessary for the management of the preferred drug list (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.[8] Despite a variety of treatments, a significant number of patients fail to meet HbA1C goals; within three years of being diagnosed with T2DM, 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 diabetes by 2050.[9] 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.[10,11] A number of therapeutic options are available for management of glycemic variances associated with diabetes.[12] 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, sodium-glucose co-transporter 2 (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.[11] Available data is 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.[11] UKPDS data also indicates reduced incidence of microvascular risk with sulfonylurea and insulin therapy. Thiazolidinediones, alpha-glucosidase inhibitors and dopamine-2 agonists have studies that suggest reduced cardiovascular disease events but additional data are needed.[11] The effects of many of the AHAs on long-term complications of T2DM remain unknown.

Clinical Efficacy:

Concomitant canagliflozin and metformin was studied in 5 phase 3, published trials including in over 4,300 patients. No phase 3 fixed dose combination trials have been conducted; however, phase 1 and phase 2 trials demonstrated bioequivalence of the fixed canagliflozin and metformin combinations to individual administration of each agent together. Trials included adult patients (mean age of 56) with mean baseline HbA1cs between 7.8% and 8.1% with normal renal function or mildly reduced renal function. Trial durations ranged from 26-104 weeks. Patients were allowed to receive rescue therapy for hyperglycemia if pre-defined fasting plasma glucose (FPG) or HbA1c values were met. Study design, inclusion and exclusion criteria and primary endpoints were similar for all studies. The primary outcome measure was change in HbA1c from baseline. Key secondary endpoints were number of patients obtaining an HbA1c less than 7% and change in weight.

Forst, et al.
Canagliflozin 100 mg once daily and canagliflozin 300 mg once daily were studied in a placebo-controlled trial of 342 patients on background metformin [≥ 2,000 mg daily (or 1,500 mg daily if unable to tolerate higher doses)] and pioglitazone (30-45 mg daily) in a good quality trial.[2] At baseline, patients had inadequately controlled HbA1c (mean value of 7.9%) with normal renal function. The primary outcome was change in HbA1c from baseline at 26 weeks, with a secondary outcome of change in HbA1c at 52 weeks. Patients in the placebo groups were switched to sitagliptin 100 mg once daily to maintain blinding for weeks 26-52. Efficacy comparisons were not analyzed for the placebo group beyond 26 weeks. Both canagliflozin arms were had significantly lower HbA1c at 26 weeks compared to baseline. HbA1c reductions were -0.89%, -1.03% and -0.26% for canagliflozin 100 mg, canagliflozin 300 mg and placebo, respectively. At 52 weeks, HbA1c lowering was maintained for both canagliflozin groups. Significantly more patients taking canagliflozin 100 mg or 300 mg obtained an HbA1c less than 7%, with a number needed to treat (NNT) of 3 and 7, respectively, at 26 weeks. Weight loss in both canagliflozin arms was significantly greater statistically relative to placebo. Significant decreases in systolic blood pressure were also found in the canagliflozin 100 mg (-5.3 mmHg) and canagliflozin 300 mg (-4.7 mmHg) arms compared to placebo (-1.2 mmHg). Increases in HDL-C were significantly higher, and dose related, in both canagliflozin groups compared to placebo at week 26. Non-significant, dose-related increases from baseline in LDL-C were seen in canagliflozin groups relative to placebo at week 26 and small further increases seen at 52 weeks.

CANTATA-D
In this good-quality trial, canagliflozin 100 mg daily and canagliflozin 300 mg daily were compared to sitagliptin 100 mg daily or placebo/sitagliptin in T2DM patients also taking metformin.[3] This was a randomized controlled trial consisting of four phases; a 2 week single-blind, placebo run in period, a 26 week placebo- and active-controlled, double-blind treatment period (period 1), a 26 week active- controlled, double-blind treatment period (period 2) and 4 week follow-up period. After 26 weeks, placebo patients were switched to sitagliptin 100 mg daily in a blinded fashion. Results for sitagliptin were only calculated for patients taking the drug from day 1. The primary endpoint was change in baseline HbA1c compared to placebo at 26 weeks. The primary hypothesis as the comparison of canagliflozin to placebo and the key secondary hypothesis was the non-inferiority of both doses of canagliflozin to sitagliptin at 52 weeks. At 26 weeks, both canagliflozin groups significantly lowered HbA1c compared to placebo (-0.79%, -0.94%, -0.17%, respectively; $p<0.001$). At 52 weeks, canagliflozin 100 mg was non-inferior to sitagliptin and canagliflozin 300 mg was superior to sitagliptin. A higher percentage of patients obtained an HbA1c less than 7% in the canagliflozin 300 mg group compared to the canagliflozin 100 mg or sitagliptin groups. At 52 weeks, patients in both canagliflozin arms had statistically significant reductions in body weight compared to sitagliptin ($p<0.001$). A significant decrease in systolic blood pressure compared to sitagliptin was also seen in

both canagliflozin groups, with decreases ranging from -2.9 to -4.0 mmHg. Small increases in LDL cholesterol and HDL were seen in both canagliflozin arms. Less patients in either canagliflozin arm required hyperglycemic rescue compared to sitagliptin or sitagliptin/placebo groups.

CANTATA-MSU

This was a fair-quality trial comparing canagliflozin 100 mg daily and canagliflozin 300 mg daily in a placebo-controlled trial in T2DM patients on background metformin and a sulfonylurea.[4] Patients were inadequately controlled with an mean HbA1c of 8.1% and 66% of patients were obese. The primary endpoint was change in HbA1c from baseline at 26 weeks, with a secondary endpoint of change in HbA1c at 52 weeks. At week 26, both groups of canagliflozin were superior to placebo, with HbA1c lowering from baseline of -0.85%, -1.06% and -0.13%, respectively. The number of patients obtaining an HbA1c less than 7% was greater in both canagliflozin groups at 26 and 52 weeks (NNT 3 at 26 weeks, no p-value reported at 52 weeks). At 52 weeks, the number of patients obtaining an HbA1c goal decreased in both canagliflozin groups and slightly improved in the placebo group. A small but statistically significant 2-3 kg weight loss was observed in both canagliflozin groups relative to placebo at 26 weeks, but was not observed at 52 weeks. Reduction in lipids and diastolic and systolic blood pressure were not statistically different between either canagliflozin arm compared to placebo.

Schernthaner, et al.

A 52-week, direct comparative study of canagliflozin 300 mg daily and sitagliptin 100 mg daily, with background metformin and sulfonylurea therapy, was studied in the CANTATA-D2 trial.[5] This was a fair quality, phase 3, double-blind, randomized trial of 755 patients with T2DM inadequately controlled on metformin and sulfonylurea therapy. Included patients had a mean duration of diabetes of 9.6 years with a mean HbA1C of 8.1%. The primary endpoint was change in baseline HbA1C at week 52. Canagliflozin was superior to sitagliptin in the primary endpoint (-1.03% vs. -0.66%, respectively). Improvements in FPG, body weight and systolic blood pressure were significantly greater with canagliflozin compared to sitagliptin. When HbA1C changes were analyzed according to baseline A1C subgroups, the greatest difference was shown in those with the highest baseline A1cs ($\geq$9.0%). The overall discontinuation rate was high and occurred in 44% of the sitagliptin group and 33% in the canagliflozin group.

Cefalu, et al.

In a phase 3, double-blind, active-controlled, non-inferiority, randomized-controlled study, canagliflozin 100 mg daily and canagliflozin 300 mg daily were compared to glimepiride, 6-8 mg daily, in patients (n=1450) inadequately controlled on metformin (CANTATA-SU).[7] Mean patient age was 56 years with a mean baseline HbA1C of 7.8%. The study treatment duration was 52 weeks and the primary endpoint was change in HbA1C at week 52. Both canagliflozin 100 mg and 300 mg arms were non-inferior to glimepiride, and canagliflozin 300 mg was shown to be superior to glimepiride. Hemoglobin A1C changes were -0.82%, - 0.93%, -0.81% for canagliflozin 100 mg, canagliflozin 300 mg and glimepiride, respectively. The percent of patients obtaining an A1C less than 7% was similar between groups. Both canagliflozin arms had statistically significant decreases in body weight compared to the glimepiride group.

Leiter, et al.

This study updates the previous study with results from the extension period. The study consisted of a 2 week, single blind, placebo run-in, a 52 week, double-blind, core treatment period (results presented above), followed by a 52 week, double-blind, extension period. Patients (n=1450) were randomized to canagliflozin 100 mg daily, canagliflozin 300 mg daily or glimepiride 6-8 mg daily.[6] Patients were an average age of 56 years old, mean baseline HbA1c of 7.8% and had normal renal function. The primary endpoint was change in HbA1c from baseline at 52 weeks. Key secondary endpoints were change in HbA1c from baseline at 104 weeks, changes in weight and percent of patients obtaining an HbA1c of less than 7% at 104 weeks. There was no pre-specified testing conducted at week 104; therefore, non-inferiority and superiority testing could not be done. Hemoglobin A1c reductions were -0.65% for canagliflozin 100 mg, -0.74% for canagliflozin 300

mg and -0.55% for glimepiride. Patients in all groups who met HbA1c goals of less than 7% at 26 weeks were able to maintain HbA1c to 104 weeks. Small decreases in systolic and diastolic blood pressure were demonstrated out to 104 weeks. There was an increase in LDL-C for both canagliflozin groups (11.2% and 14.3% for 100 mg and 300 mg, respectively) and glimepiride (6.3%).

Limitations to CM studies include the titration of background therapy based on clinical requirements without standardized protocol. Some trials had high attrition rates, which could influence true effect of therapy. Some studies failed to report confidence intervals with data, which can limit interpretation of magnitude of treatment effect. The last observation carried forward imputation was used to provide results for missing data in all studies. This method may introduce assessment bias, especially in circumstances where there is a higher attrition rate in the active comparator group, which assumes no change, potentially overestimating the true treatment effect of CM.

Clinical Safety:

In studies of 6,177 T2DM patients receiving canagliflozin, the most common adverse effects associated with the canagliflozin arms were fatigue, female genital mycotic infections, urinary tract infections, increased urination and male genital mycotic infections. Long term effects of commonly experienced adverse effects are unknown and could be problematic. Hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration, occurred as a result of the osmotic diuresis properties of canagliflozin, are also observed. Patients at increased risk of osmotic diuresis are those over 75 years of age, those on concomitant loop diuretic therapy, and those with moderate renal impairment (estimated glomerular filtration rate [eGFR] 30 to less than 60 mL/min/1.73 m^2). Dose-related increases in serum creatinine were also noted in these trials. Slightly higher rates of hypoglycemia occurred in the canagliflozin arms compared to placebo and were more common when canagliflozin was combined with insulin or sulfonylureas. Pooled data on the risk of pancreatitis with canagliflozin show the incidence to be 0.9, 2.7 and 0.9 per 1000 patient years of exposure for comparators, canagliflozin 100 mg, and canagliflozin 300 mg, respectively. Lab abnormalities were seen in patients randomized to canagliflozin, including elevation in hemoglobin and dose-related increases in potassium, magnesium and phosphate. Increased LDL cholesterol levels of 4.4 mg/dL (4.5%) and 8.2 mg/dL (8.0%) also occurred in the 100 mg and 300 mg canagliflozin arms, respectively.

Metformin has most commonly been associated with the adverse reactions of diarrhea, nausea, vomiting, flatulence, asthenia, indigestion, abdominal discomfort and headache. Long-term therapy may be associated with decreases in vitamin $B_{12,}$ which is rarely clinically significant. Rarely, lactic acidosis may occur in the setting of acute kidney injury.

Conclusion:

In conclusion, there is no evidence that adding metformin to canagliflozin reduced microvascular outcomes, macrovascular outcomes or mortality. There is moderate strength of evidence that adding canagliflozin to metformin lowers HbA1c by an additional -0.65% to -1.06% in published efficacy studies ranging from 26 to 52 weeks. Lowering of HbA1c was greatest at 26 weeks with decreasing efficacy at 104 weeks. Canagliflozin is unlikely to cause hypoglycemia and has demonstrated positive effects on FPG, BP, HDL and body weight while causing dose-related increases in LDL levels. Common adverse reactions associated with canagliflozin include female mycotic infections, urinary tract infections and increased urination. The cardiovascular risk of major adverse cardiac events associated with canagliflozin are being evaluated in the CANagliflozin cardio Vascular Assessment Study (CANVAS). Results should be available in 2017.

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
Forst, et al 2014[2] DB, Phase 3, RCT 74 Centers and 11 Countries	1. Canagliflozin 100 mg PO daily (C100) 2.Canaglilfozin 300 mg PO daily (C300) 3. Placebo (P)∞ * Patients underwent a 2-week single-blind run in period. *Patients were on background metformin and pioglitazone. * Trial was 52 weeks- 26 weeks of core treatment and 26 weeks extension study ∞ Switched to sitagliptin 100mg after 26 weeks to maintain blinding. Only included in 26 week analysis.	**Demographics:** Age (mean): 57 years Female: 37% HbA1c (mean): 7.9% BMI (mean): 32.5 kg/m^2 **Inclusion Criteria:** Patients ≥18 and ≤80 years old, HbA1c of ≥7-≤10.5% with T2DM and on stable doses of metformin and pioglitazone (if not on max tolerated doses then entered a dose stabilization period of 12 weeks before entering study), FPG <270 mg/dL at week-2 and fasting fingerstick glucose ≥110 mg/dL and <270 mg/dL on day 1. **Exclusion Criteria:** Repeated FPG and/or SMBG of ≥270 mg/dL during pretreatment phase; T1DM; cardiovascular disease; uncontrolled hypertension; eating disorder; eGFR <55	1.113 (104) (96)* Attrition 15% 2.114 (101) (89)* Attrition 21.9% 3.115 (91) (78)* Attrition 32.2% *Per protocol population for extension period	**<u>Primary Endpoint</u>** **Change in HbA1c at 26 weeks:** C100: -0.89% C300: -1.03% P: -0.26% C100 vs. P: -0.62% C300 vs. P: -0.76% p<0.001 for both comparisons (CI not given) **<u>Secondary Outcomes</u>** **Change in HbA1c at 52 weeks:** C100: -0.92% C300: -1.03% **Patients Obtaining HbA1c <7% at 26 weeks:** C100: 46.9% C300: 64.3% P: 32.5% C100 vs P: P<0.01 C300 vs P: p<0.001 **Changes in Weight at week 26:** C100: -2.5 kg C300: -3.5 kg	NA NA C100 vs. P: ARR: 14% NNT: 7 C300 vs. P: ARR:32% NNT: 3	**Discontinuations due to Adverse Events at 52 weeks:** C100: 2 (1.8%) C300: 5 (4.4%) P: 7 (6.1%) p-value not reported **Hypoglycemia at 52 weeks:** C100: 5 (4.4%) C300: 7 (6.1%) P: 7 (6.1%) p-value not reported **Male genital mycotic infections:** C100: 3 (3.9%) C300: 3 (4.8%) P: 0 (0%) p-value not reported **Female genital mycotic infections:** C100: 6 (16.7%) C300: 11 (21.6%) P: 3 (7.7%) p-value not reported	NA	**Quality rating:** Good **Internal Validity:** <u>Selection:</u> Interactive voice response system/interactive web response system was used. <u>Performance:</u> Patients and caregivers blinded to treatment. <u>Detection:</u> Assessors were blinded to treatment. <u>Attrition:</u> Attrition at 26 weeks (8-21%); mITT analysis with LOCF. **External Validity:** <u>Recruitment:</u> Patients from 74 centers and 11 countries were included. <u>Patient Characteristics:</u> More females were in the C300 group and a lower percentage was Asian. Greater than 90% of patients were on ≥2000 mg metformin and 68% were on 30 mg of pioglitazone. Patients had normal renal function. <u>Outcomes:</u> Accepted surrogate end-point used. Data on long-term health outcomes are lacking.

		ml/min (or <60 ml/min/1.73m^2 based on metformin labeling recommendations); or elevated SCr		P: -0.1 kg C100 and C300 vs P: P<0.001	NA	**Urinary Tract Infections:** C100: 6 (5.3%) C300: 9 (7.9%) P: 9 (7.8%) p-value not reported		
Lavalle-Gonzáles, et al 2013[3] (CANTATA-D) DB, Phase 3, RCT 169 Centers and 22 Countries	1. Canagliflozin 100 mg PO daily (C100) 2.Canaglilfozin 300 mg PO daily (C300) 3. Sitagliptin 100 mg PO daily(S) 4. Placebo (P)∞ * Patients underwent a 2-week single-blind run in period. *Patients were on background metformin * Trial was 52 weeks ∞ Switched to sitagliptin 100mg after 26 weeks.	**Demographics:** Age (mean): 55 years Female: 53% HbA1c (mean): 7.9% BMI (mean): 31.8 kg/m^2 **Inclusion Criteria:** Patients ≥18 and ≤80 years old, HbA1c of ≥7-≤10.5% with T2DM and on stable doses of metformin for at least ≥8 weeks before randomization and FPG <268 mg/dL at week-2 and fasting fingerstick glucose ≥109 mg/dL and <268 mg/dL on day 1. **Exclusion Criteria:** Repeated FPG and/or SMBG of ≥268 mg/dL during pretreatment phase; T1DM; cardiovascular disease; uncontrolled HTN; eGFR <55 ml/min or elevated SCR; treatment with peroxisome proliferator-activated receptor ϒ agonist, insulin, other SGLT2 inhibitor or other antihyperglycemic agents.	1.368 (322) (298)* Attrition 19% 2.367 (323) (299)* Attrition 19% 3.366 (319) (285)* Attrition 22% 4.183 (155) (138)* Attrition 25% *Per protocol numbers for phase II period	**<u>Primary Endpoint</u>** **Change in HbA1c at 26 weeks:** C100: -0.79% C300: -0.94% S: -0.82 % P: -0.17% C100 vs. P: -0.62% C300 vs. P: -0.77% p<0.001 for both comparisons (CI not given) **<u>Secondary Outcomes</u>** **Change in HbA1c at 52 weeks:*** C100: -0.73% C300: -0.88% S: -0.73% C100 vs. S: 0% (95% CI -0.12 to 0.12, for non-inferiority) C300 vs. S: -0.15% (95%CI -0.27 to -0.03, for superiority) **Patients Obtaining HbA1c <7% at 26 weeks:** C100: 45.5% C300: 57.8% S: 54.5% P: 29.0% P=0.000 for C100 and C300 vs placebo **Changes in Weight at week 52:** C100: -3.3 kg C300: -3.6 kg	NA NA C100 vs.P: ARR: 17% NNT: 6 C300 vs. P: ARR:29% NNT: 3	**Discontinuations due to Adverse Events at 52 weeks:** C100: 19 (5.2%) C300: 12 (3.3%) S: 16 (4.4%) P: 8 (4.4%) p-value not reported **Hypoglycemia at 52 weeks:** C100: 25 (6.8%) C300: 25(6.8%) S: 15 (4.1%) P: 5 (2.7%) p-value not reported **Male genital mycotic infections:** C100: 9 (5.2%) C300: 4 (2.4%) S: 2 (1.2%) P: 1 (1.1%) p-value not reported **Female genital mycotic infections:** C100: 20 (9.9%) C300: 22 (11.3%) S: 5 (2.6%) P: 1 (1.1%) p-value not reported **Urinary Tract Infections:** C100: 29 (7.9%) C300: 18 (4.9%) S: 23 (6.3%) P: 12 (6.6%)	NA	**Quality rating:** Good **Internal Validity:** <u>Selection:</u> Used an interactive voice response system Computer-generated schedule. <u>Performance:</u> Patients and caregivers blinded to treatment. <u>Detection:</u> Assessors were blinded to treatment. <u>Attrition:</u> High attrition up to 52 week (19-25%); mITT analysis with LOCF. **External Validity:** <u>Recruitment:</u> Patients from 169 centers and 22 countries were included. <u>Patient Characteristics:</u> Patients had normal or mildly reduced renal function and were overweight. <u>Outcomes:</u> Accepted surrogate end-point used. Data on long-term health outcomes are lacking.

				S: -1.1 kg P: -1.1 kg C100 and C300 vs P: P<0.001 *Only includes patients originally randomized to sitagliptin.	NA	p-value not reported		
Wilding, et al 2013[4] (CANTATA-MSU) DB, PC,Phase 3, RCT 85 Centers and 11 Countries	1. Canagliflozin 100 mg PO daily (C100) 2.Canaglilfozin 300 mg PO daily (C300) 3. Placebo (P) * Patients underwent a 2-week single-blind run in period. *Patients were on background metformin and sulfonylurea * Trial was 52 weeks- 26 weeks of core treatment and 26 weeks extension study	**Demographics:** Age (mean): 57 years Female: 49% HbA1c (mean): 8.1% BMI (mean): 33.1 kg/m^2 **Inclusion Criteria:** Patients ≥18 and ≤80 years old, HbA1c of ≥7-≤10.5% on maximally or near-maximally effective doses of metformin and a sulfonylurea with T2DM. **Exclusion Criteria:** History of diabetic ketoacidosis, T1DM, repeated FPG and/or SMBG of ≥268 mg/dL during pretreatment phase, history of ≥1 severe hypoglycemia episodes within 6 months before screening, eGFR <55 ml/min/1.73m^2 (or <60 ml/min/1.73m^2 based on metformin labeling recommendations), elevated SCr, uncontrolled HTN or us of other AHA agents within 12 weeks prior to screening.	1.157 (129) (109)* Attrition 30% 2. 156 (129) (111)* Attrition 29% 3.156 (123) (90)* Attrition 42% *Per protocol population for extension period	**<u>Primary Endpoint</u>** **Change in HbA1c at 26 weeks:** C100: -0.85% C300: -1.06% P: -0.13% P<0.001 C100 vs. P: -0.71% (95% CI -0.90 to -0.52) C300 vs. P: -0.92% (95% CI -1.11 to -0.73) p<0.001 for both comparisons **<u>Secondary Outcomes</u>** **Change in HbA1c at 52 weeks:** C100: -0.74% C300: -0.96% P: 0.01% C100 vs. P: -0.75% (95% CI -0.95 to -0.55) C300 vs. P: -0.97% (95% CI -1.17 to -0.77) **Patients Obtaining HbA1c <7% at 26 weeks:** C100: 43.2% C300: 56.6% P: 18.0% P<0.001 for C100 and C300 vs placebo **Patients Obtaining HbA1c <7% at 52weeks:** C100: 39.4% C300: 52.6%	NA NA C100 vs.P: ARR: 25% NNT: 4 C300 vs. P: ARR:39% NNT: 3 NA	**Discontinuations due to Adverse Events at 52 weeks:** C100: 11 (7.0%) C300: 12 (7.7%) P: 7 (4.5%) p-value not reported **Hypoglycemia at 52 weeks:** C100: 53 (33.8%) C300: 57 (36.5%) P: 28 (17.9%) p-value not reported **Male genital mycotic infections:** C100: 6 (7.9%) C300: 5 (5.7%) P: 1 (1.3%) p-value not reported **Female genital mycotic infections:** C100: 15 (18.5%) C300: 13 (18.8%) P: 4 (5.0%) p-value not reported **Urinary Tract Infections:** C100: 13 (8.3%) C300: 13 (8.3%) P: 12 (7.7%) p-value not reported	NA	**Quality rating:** Fair **Internal Validity:** <u>Selection:</u> Interactive voice response system/interactive web response system based on a computer-generated schedule. <u>Performance:</u> Patients and caregivers blinded to treatment. <u>Detection:</u> Assessors were blinded to treatment. <u>Attrition:</u> High attrition up to 26 week (17-21%) and at 52 weeks (29-42%); mITT analysis with LOCF. **External Validity:** <u>Recruitment:</u> Patients from 85 centers and 11 countries were included. <u>Patient Characteristics:</u> Patients in c300 group had 6% more males and patients in placebo group had had diabetes for a year longer than those in other groups. A majority of patients were considered obese (66%). <u>Outcomes:</u> Accepted surrogate end-point used. Data on long-term health outcomes are lacking.

				P: 18.7% **Changes in Weight at week 52:** C100: -2.0 kg C300: -3.1 kg S: -1.1 kg P: -1.0 kg	NA			
Schernthaner et al[5] (CANTATA-D2) Phase 3, RCT, DB, active control, non-inferiority trial 140 Center and 17 countries	1. Canagliflozin 300 mg PO daily (C300) 2. Sitagliptin 100 mg PO daily (S100) * Both groups on background metformin and sulfonylurea *52 weeks with a 2 week single-blind placebo run-in	**Demographics:** Age: 56 years Female: 44.1% HbA1c (mean): 8.1% BMI (mean): 31.6 kg/m^2 **Inclusion:** Subjects 18 years and older, T2DM, on maximally or near maximally effective doses of metformin (2000 mg/day [or 1,500 mg/day if unable to tolerate a higher dose]) and sulfonylurea (at half-maximal labeled dose or more) and A1C ≥7.0% and ≤ 10.5%. **Exclusion:** Prior AHA therapy other than metformin and sulfonylurea up to 12 weeks prior to study enrollment, repeated fasting plasma glucose or fasting self-monitored blood glucose measurements >16.7 mmol/L (300 mg/dL) or both during pretreatment phase, T1DM, uncontrolled HTN, cardiovascular disease and eGFR <55 mL/min/1.73m^2.	1. 377 (254) Attrition 33% 2. 378 (210) Attrition 44%	**<u>Primary Endpoint</u>** **Change from baseline in HbA1C at 52 weeks**: C300: -1.03% S100: -0.66% LS means: -0.37 (95% CI -0.50 to -0.25) non-inferiority and superiority was achieved) **<u>Secondary Outcomes</u>** **Subjects reaching A1C <7.0%:** C300: 47.6% S100: 35.3% **Changes in Baseline body weight:** C300: -2.3 kg (-2.5%) S100: 0.1 kg (0.3%) LS Mean Change: -2.8%, p<0.001	NA ARR: 12.3 NNT: 8 NA	**Discontinuations due to Adverse Events:** C300: 20 (5.3%) S100: 11 (2.9%) p-value not reported **Hypoglycemia:** C300: 163 (43.2%) S100: 154 (40.7%) p-value not reported **Urinary tract infection:** C100: 15 (4.0%) S100: 21 (5.6%) p-value not reported **Males genital mycotic infection:** C300: 19 (9.2%) S100: 1 (0.5%) p-value not reported **Female genital mycotic infection:** C300: 26 (15.3%) S100: 7 (4.3%) p-value not reported	NA	**Quality Rating:** Fair <u>Internal Validity:</u> Selection: Patients were randomized via interactive voice response system/interactive web response system and computer generated randomization schedule. High and different levels of attrition may have affected the ability to maintain randomization. <u>Performance:</u> Study was double-blind with study personnel remaining blinded to treatment allocation. Detection: Investigators and local sponsor personnel were blinded to treatment assignment. <u>Attrition:</u> mITT analysis was used with LOCF for missing data. Potential for bias due to only 61% of patients completing the 52 week study. **External Validity:** <u>Recruitment:</u> 140 centers in 17 countries. <u>Patient Characteristics:</u> Patients with almost 10 years of diabetes and moderate A1cs were included. Not studied in newly diagnosed and those with cardiovascular disease. <u>Outcomes:</u> Accepted surrogate end-point used. Data on long-term health outcomes are lacking.

Leiter, et al 2013[6]	1. Canagliflozin	**Demographics:** Age: 56 yrs	1. 483 (395) (343)*	**<u>Secondary Outcomes*</u>** **Change from Baseline in HbA1C at**		**Discontinuations due to Adverse Events:**		**Quality Rating:** Fair

(CANTATA-SU ext.) Phase 3, DB, active-controlled, non-inferiority, RCT 157 centers and 19 countries	100mg PO daily (C100 2. Canagliflozin 300mg PO daily (C300 3. Glimepiride 6-8mg PO daily (G) * All patients on background metformin * 52 weeks with 2-week placebo run-in period, followed by 52 week extension trial.	Male: 52% HbA1C (mean): 7.8% BMI (mean): 31.0 kg/m^2 **Inclusion:** T2DM, 18-80 years old, A1C ≥7.0 and ≤9.5%, and stable metformin dose for at least 10 weeks. **Exclusion:** History of severe hypoglycemia requiring treatment, FPG ≥268 mg/dL (eGFR <55 ml/min/1.73 m^2, SrCr ≥1.4 mg/dL for men or SrCr ≥1.3 mg/dL for women or TZD in prior 16 weeks.	Attrition 29% 2. 485 (380) (323)* Attrition 33% 3. 482 (386) (314)* Attrition 29% *Per protocol population from extension period	**104 weeks :** C100: -0.65% C300: - 0.74% G: -0.55% (not pre-specified, therefore no p-values) C100 vs. G: -0.09% (95% CI -0.20 to -0.01%) C300 vs. G: -0.18% (95% CI -0.29 to -0.08) **Subjects reaching HbA1C <7.0% at 104 weeks:** C100: 42.5% C300: 50.2% G: 43.9% p-value not given **Changes in Baseline body weight at 104 weeks:** C100: - 3.6 kg C300: - 3.6 kg G: 0.8 kg *Primary outcome reported in separate study below (Cefalu, et al)	NA NA NA	C100: 30 (6.2%) C300: 46 (9.5%) G: 35 (7.3%) p-value not reported **Hypoglycemia:** C300: 3 (<1%) C100: 2 (<1%) G: 15 (3%) p-value not reported **Urinary tract infection:** C100: 51 (10.6%) C300: 42 (8.7%) G: 33 (6.8%) p-value not reported **Males genital mycotic infection:** C100: 24 (9.5%) C300: 22 (9.1%) G: 5 (1.9%) p-value not reported **Female genital mycotic infection:** C100: 32 (13.9%) C300: 38 (15.6%) G: 6 (2.7%) p-value not reported	NA	**Internal Validity:** Selection: Patients were randomized via interactive voice response system/interactive web response system and computer generated randomization schedule. Performance: Study was double-blind and efforts were made to maintain blinding during titration. Detection: Investigators and local sponsor personnel were blinded to treatment assignment. Attrition: mITT analysis was used with LOCF for missing data. Overall attrition was 18-22% with similar rates between the groups. **External Validity:** Recruitment: 157 centers in 17 countries. Patient Characteristics: Patients had an approximate 7 year history of diabetes that were predominately white with normal renal function. Mean glimepiride dose during extension phase was 5.6 mg. Outcomes: Accepted surrogate end-point used. Data on long-term health outcomes are lacking.
Cefalu, et al 2013[7] (CANTATA-SU) Phase 3, DB, active-controlled, non-inferiority, RCT 157 centers	1. Canagliflozin 100mg PO daily (C100 2. Canagliflozin 300mg PO daily (C300 3. Glimepiride 6-8mg PO daily (G) * All patients on background metformin	**Demographics:** Age: 56 yrs Male: 52% HbA1C (mean): 7.8% BMI (mean): 31.0 kg/m^2 **Inclusion:** T2DM, 18-80 years old, HbA1C ≥7.0 and ≤9.5%, and stable metformin dose for a least 10 weeks. **Exclusion:** History of severe	1. 483 (395) Attrition 18% 2. 485 (380) Attrition 22% 3. 482 (386) Attrition 20%	**<u>Primary Endpoint</u>** **Change in HbA1C from baseline to week 52 :** C100: -0.82% C300: - 0.93% G: -0.81% LS Mean Change C100: -0.01% (95% CI -0.11 to -0.09) C100 non-inferior to glimepiride LS Mean Change C300: -0.12%		**Urinary tract infection:** C100: 31 (6%) C300: 31 (6%) G: 25 (5%) p-value not reported **Males genital mycotic infection:** C100: 17 (7%) C300: 20 (8%) G: 3 (1%) p-value not reported **Female genital mycotic**	NA	**Quality Rating:** Fair **Internal Validity:** Selection: Patients were randomized via interactive voice response system/interactive web response system and computer generated randomization schedule. Performance: Study was double-blind and efforts were made to maintain blinding during titration. Detection: Investigators and local sponsor personnel were blinded to treatment assignment.

and 19 countries	* 52 weeks with 2-week placebo run-in period,	hypoglycemia requiring treatment, FPG ≥268 mg/dL (eGFR <55 ml/min/1.73 m^2, SrCr ≥1.4 mg/dL for men or SrCr ≥1.3 mg/dL for women or TZD in prior 16 weeks.		(95% CI -0.22 to -0.02) C300 superior to glimepiride (no p-value given) **Secondary Outcomes** **Subjects reaching HbA1C <7.0% at 52 weeks:** C100: 54% C300: 60% G: 56% p-value not given **Changes in Baseline body weigh at 52 weeks:** C100: -3.7 kg (4.2%) C300: -4.0kg (4.7%) G: 0.7 kg (1%) P<0.0001 for both doses	NA NA NA	**infection:** C100: 26 (11%) C300: 34 (14%) G: 5 (2%) p-value not reported **Severe Hypoglycemia:** C300: 3 (<1%) C100: 2 (<1%) G: 15 (3%) p-value not reported **Withdrawal due to Adverse Events:** C100: 25 (5%) C300: 32 (7%) G: 28 (6%) p-value not reported		Attrition: mITT analysis was used with LOCF for missing data. Overall attrition was 18-22% with similar rates between the groups. **External Validity:** Recruitment: 157 centers in 17 countries. Patient Characteristics: Patients had an approximate 7 year history of diabetes that were predominately white. Outcomes: Accepted surrogate end-point used. Data on long-term health outcomes are lacking.
Key: AEs: adverse events, BMI: body mass index, CI: confidence interval, 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, SCr: serum creatinine, T1DM: type 1 diabetes mellitus, T2DM: type 2 diabetes mellitus								

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Appendix 1: 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.

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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 as doses advanced, 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

Author: Kathy Sentena, Pharm.D.

Appendix 2: Specific Drug Information

CLINICAL PHARMACOLOGY [1]

This is a combination formulation of canagliflozin and metformin. Canagliflozin is a SGLT2 inhibitor, which reduces the reabsorption of renal glucose and increases the urinary glucose excretion. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

PHARMACOKINETICS[1]

Parameter	Canagliflozin	Metformin
Oral Bioavailability	65%	50-60%
Protein Binding	99%	negligible
Elimination	33% renal 41.5% hepatic	90% renal
Half-Life	10.6 – 13.1 hours	6.2 hours in plasma/17.6 hours in blood
Metabolism	glucuronidation	Excreted unchanged

DOSE & AVAILABILITY[1]

STRENGTH	ROUTE	FREQUENCY	DOSAGE	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
- canagliflozin 50 mg and metformin 500 mg - canagliflozin 50 mg and metformin 1,000 mg - canagliflozin 150 mg and metformin 500m g - canagliflozin 150 mg and metformin 1,000 mg	Oral	Twice daily	Take twice daily with meals. Increase dose slowly to minimize gastrointestinal side effects.	Do not use in patients with renal impairment (SrCr ≥1.5 mg/dL for males or ≥1.4 mg/dL for females). Limit dose to canagliflozin 50 mg twice daily in patients with moderate renal impairment (eGFR of 45 to <60 mL/min/1.73 m^2 or greater).	Use not recommended in patients with hepatic impairment.	Not studied	Monitor renal function more frequently in the elderly. Dose according to renal function	- N/A

DRUG SAFETY [1]

Serious (REMS, Black Box Warnings, Contraindications):

- Black box warning: The metformin component in this combination can cause lactic acidosis. The risk increases in the following conditions: renal impairment, sepsis, dehydration, excess alcohol intake, hepatic impairment, and acute congestive heart failure.
- REMS: REMS is not required for the CM.
- Contraindications: CM should not be used in patients with renal impairment, ESRD, on dialysis, metabolic acidosis (including diabetic ketoacidosis), or hypersensitivity reaction to either canagliflozin or metformin.

Warnings and Precautions:

- Advise against alcohol use due to risk of lactic acidosis. Do not use CM in patients with hepatic impairment or hypoxic states.
- Monitor renal function and only initiate CM if normal renal function is verified.
- Volume status should be monitored and hypovolemia should be corrected in patients with renal impairment, elderly, low systolic blood pressure, diuretic use, ACE inhibitors use or ARB use.
- Temporarily discontinue CM if radiologic studies with IV administration of iodinated contrast is used or if food or liquid intake is restricted.
- Potassium levels should be monitored in patients with impaired renal function and in those predisposed to hyperkalemia.
- A reduced dose of insulin or insulin secretagogues may be needed when initiating CM.
- Monitor patients for genital mycotic infections.
- Discontinue use if hypersensitivity reaction occurs.
- Metformin may decrease vitamin B12 levels.
- Increased LDL levels may occur, treat if needed.

Monitoring: Monitor renal function, potassium and vitamin B12.

Drug-Drug interactions: Cationic drugs may reduce metformin elimination. UGT inducers (rifampin) may reduce canagliflozin exposure, dose may need to be increased. Monitor digoxin levels in patients with CM.

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

Pregnancy/lactation rating: Category C. Only use CM if benefit justifies the risk. Do not use if nursing.

ADVERSE REACTIONS[1]

Adverse reactions occurring in ≥5% of patients treated with CM were: female genital mycotic infections, urinary tract infections and increased urination, diarrhea, nausea, vomiting, flatulence, asthenia, indigestion, abdominal discomfort, and headache.

Author: Kathy Sentena, Pharm.D.