

## Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors Non-Insulin Diabetes Drugs

### Executive Summary

- There are currently three available agents (canagliflozin, dapagliflozin, and empagliflozin) and three fixed-dose combinations (canagliflozin/metformin, dapagliflozin/metformin XR, and empagliflozin/linagliptin).
- Since the SGLT2 inhibitors were first reviewed in May 2013, each has been reviewed individually and all are currently nonformulary.
- Step therapy applies: patients must first try metformin or a sulfonylurea (SU) and a d (DPP-4) inhibitor.
- There have been no head-to-head studies between any of the SGLT2 inhibitors.
- When used as monotherapy, SGLT2 inhibitors lowered A1c by ~0.4% to 1.3%.
- As part of dual therapy, SGLT2 inhibitors lowered A1c by ~0.5% to 2%.
- As part of triple therapy, SGLT2 inhibitors lowered A1c as low as 0.3% (with sitagliptin and metformin) and as high as 1% [canagliflozin with metformin/SU or thiazolidinediones (TZD)] or (dapagliflozin + insulin +/- oral antidiabetic agents).
- In general, SGLT2 inhibitors decrease triglycerides, increase low-density lipoprotein and high-density lipoprotein, and decrease weight.
- SGLT2 inhibitors consistently provided small but clinically significant decreases in systolic blood pressure (~4-6 mmHg), regardless of monotherapy or adjunctive use.
- SGLT2 inhibitors should be avoided in renal impairment.
- The most common adverse drug reactions are genital mycotic infections and urinary tract infections.
- SGLT2 inhibitors offer another oral option as add-on therapy when other agents no longer provide adequate glycemic control.
- There is a high degree of therapeutic interchangeability between canagliflozin, dapagliflozin, and empagliflozin.

### Previous Uniform Formulary Review

The SGLT2 inhibitors were first reviewed in May 2013. Canagliflozin was designated nonformulary. Dapagliflozin was reviewed in May 2014 and empagliflozin was reviewed in February 2015. Both were designated nonformulary. Step therapy applies to the subclass, which requires a trial of metformin or a SU and a preferred DPP-4 inhibitor (i.e., sitagliptin) prior to the use of a SGLT2 inhibitor.

### Table 1: Current Formulary Status

Note: Invokamet, Xigduo XR, and Glyxambi have not been reviewed.

SGLT2 Inhibitors		
BCF	None	
UF	None	
NF	Canagliflozin (Invokana) Dapagliflozin (Farxiga) Empagliflozin (Jardiance)	Must try metformin or a SU first AND a DPP-4 inhibitor; 180-day look back

Table 2: Sodium-Glucose Co-Transporter 2 Inhibitors Available in the United States<sup>1-6</sup>

Active Ingredient	Brand (Manufacturer)	Strengths	FDA Approval Date	Patent Expiration Date
Canagliflozin	Invokana (Janssen)	100 mg, 300 mg	3/29/2013	2024
Canagliflozin/ metformin	Invokamet	50/500 mg; 50/1000 mg 150/500 mg; 150/1000 mg	8/8/2014	
Dapagliflozin	Farxiga (BMS/AstraZeneca)	5 mg, 10 mg	1/8/2014	-
Dapagliflozin/ metformin XR	Xigduo XR (BMS/AstraZeneca)	5/500 mg; 5/1000 mg 10/500 mg; 10/1000 mg	10/29/2014	
Empagliflozin	Jardiance (Boehringer Ingelheim)	10 mg, 25 mg	8/1/2014	
Empagliflozin/ linagliptin	Glyxambi (Boehringer Ingelheim)	10/5 mg, 25/5 mg	1/30/15	

## Indications

All SGLT2 inhibitors are indicated as adjunct therapy to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).<sup>4-6</sup>

## Efficacy

The safety and efficacy of canagliflozin was studied in a series of nine phase 3, double-blind, randomized, controlled multinational studies enrolling approximately 10,300 patients.<sup>1,7-9</sup> The studies varied in length from 18 to 104 weeks and examined canagliflozin in patients with T2DM as monotherapy (with placebo), dual therapy (one with sitagliptin and one with glimepiride), and as triple therapy (one with sitagliptin, three with placebo). There have also been studies conducted in special populations (one with elderly patients and one in patients with moderate renal impairment). Across all studies, canagliflozin was used in combination with diet and exercise and evaluated against active comparators including metformin, a SU, metformin/SU combination, metformin/TZD combination, and with insulin.<sup>1,7-9</sup>

Eleven studies with dapagliflozin were included in this review, including four monotherapy studies, six dual therapy studies (four with metformin, one with a TZD, and one with a SU), and two triple therapy studies (one with sitagliptin/metformin and one with insulin plus other oral agents). The studies ranged from 12 to 156 weeks.<sup>10-20</sup> Similar active comparators were evaluated in the dapagliflozin studies, which included metformin, a SU, TZD, DPP-4 inhibitor, and insulin.

Eight studies with empagliflozin were included in this review: one monotherapy study, three dual therapy studies (two with metformin and one with a sulfonyleurea), three triple therapy studies (one with SU/metformin, one with TZD/metformin, and one with insulin/metformin) and one quadruple therapy study (insulin/metformin/SU). The studies ranged from 24-104 weeks.<sup>3,6,21-30</sup> As seen in the canagliflozin and dapagliflozin studies, active comparators included metformin, a SU, TZD, DPP-4 inhibitor, and insulin.

A systematic review found that SGLT2 inhibitors had a favorable effect on HbA1c levels with a mean difference of -0.66% [95% CI, -0.73% to -0.58%] when compared with placebo and an average difference of -0.06% [95% CI, -0.18% to 0.05%] when evaluated against active comparators.<sup>31</sup> A reduction in body weight was also shown with a mean difference of 1.8 kg and reductions seen in systolic blood pressure with a mean difference of 4.45 mmHg. Authors concluded there were no clinically significant differences found between the SGLT2 inhibitors in terms of glycemic control.<sup>31</sup>

## Additional Safety Concerns

- There are no major drug interactions reported to date for dapagliflozin and empagliflozin. However, canagliflozin is reported to have decreased effects when used with UGT inducers and may increase the extent of digoxin absorption.<sup>4-6</sup>
- While a 30-month safety update presented statistics that could not provide a causal relationship between use of dapagliflozin and bladder cancer, labeling does include a warning that dapagliflozin should not be used in patients with a history of bladder cancer.<sup>3</sup>

## References

1. Invokana (canagliflozin). Janssen Pharmaceuticals, Inc. Academy of Managed Care Pharmacy Dossier. April 2015.
2. Farxiga (dapagliflozin). AstraZeneca. Academy of Managed Care Pharmacy Dossier. April 2015.
3. Jardiance (empagliflozin). Boehringer Ingelheim Pharmaceuticals, Inc. Academy of Managed Care Pharmacy Dossier. October 2014.
4. Invokana (canagliflozin). Product labeling. Janssen Pharmaceuticals, Inc. March 2015.
5. Farxiga (dapagliflozin). Product labeling. AstraZeneca. January 2014.
6. Jardiance (empagliflozin). Product labeling. Boehringer Ingelheim Pharmaceuticals, Inc. August 2014.
7. Scherthaner G, Gross JL, Rosenstock J, et al. Canagliflozin Compared With Sitagliptin for Patients With Type 2 Diabetes Who Do Not Have Adequate Glycemic Control With Metformin Plus Sulfonyleurea: A 52-week randomized trial. *Diabetes Care*. 2013;36(9):2508-2515.
8. Stenlöf K, Cefalu W, Kim KA, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. *Diabetes, Obesity and Metabolism*. 2013;15(4):372-382.
9. Yale JF, Bakris G, Cariou B, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. *Diabetes, Obesity and Metabolism*. 2013;15(5):463-473.
10. Wilding JP, Norwood P, T'joen C, et al. A study of dapagliflozin in patients with type 2 diabetes receiving high doses of insulin plus insulin sensitizers applicability of a novel insulin-independent treatment. *Diabetes Care*. 2009;32(9):1656-1662.
11. Bailey CJ, Gross JL, Pieters A, et al. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. *The Lancet*. 2010;375(9733):2223-2233.
12. Ferrannini E, Ramos SJ, Salsali A, et al. Dapagliflozin monotherapy in Type 2 diabetic patients with inadequate glycemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase 3 trial. *Diabetes Care*. 2010;33(10):2217-2224.

13. Nauck MA, Del Prato S, Meier JJ, et al. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial. *Diabetes Care*. 2011;34(9):2015-2022.
14. Strojek K, Yoon K, Hrubá V, et al. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. *Diabetes, Obesity and Metabolism*. 2011;13(10):928-938.
15. Bailey C, Iqbal N, T'joen C, List J. Dapagliflozin monotherapy in drug-naïve patients with diabetes: a randomized-controlled trial of low-dose range. *Diabetes, Obesity and Metabolism*. 2012;14(10):951-959.
16. Henry R, Murray A, Marmolejo M, et al. Dapagliflozin, metformin XR, or both: initial pharmacotherapy for type 2 diabetes, a randomised controlled trial. *International journal of clinical practice*. 2012;66(5):446-456.
17. Jabbour SA, Whaley JM, Tirmenstein M, et al. Targeting renal glucose reabsorption for the treatment of type 2 diabetes mellitus using the SGLT2 inhibitor dapagliflozin. *Postgraduate medicine*. 2012;124(4):62-73.
18. Rosenstock J, Vico M, Wei L, et al. Effects of dapagliflozin, an SGLT2 inhibitor, on HbA1c, body weight, and hypoglycemia risk in patients with type 2 diabetes inadequately controlled on pioglitazone monotherapy. *Diabetes Care*. 2012;35(7):1473-1478.
19. Bailey CJ, Gross JL, Hennicken D, et al. Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled 102-week trial. *BMC medicine*. 2013;11(1):43.
20. Kaku K, Inoue S, Matsuoka O, et al. Efficacy and safety of dapagliflozin as a monotherapy for type 2 diabetes mellitus in Japanese patients with inadequate glycaemic control: a phase II multicentre, randomized, double-blind, placebo-controlled trial. *Diabetes, Obesity and Metabolism*. 2013;15(5):432-440.
21. Ferrannini E, Berk A, Hantel S, et al. Long-Term Safety and Efficacy of Empagliflozin, Sitagliptin, and Metformin: An active-controlled, parallel-group, randomized, 78-week open-label extension study in patients with type 2 diabetes. *Diabetes Care*. 2013;36(12):4015-4021.
22. Häring H, Merker L, Seewaldt-Becker E, et al. Empagliflozin as add-on to metformin for 24 weeks improves glycaemic control in patients with type 2 diabetes (T2DM). *Diabetes*. 2013;62(suppl 1):A282.
23. Häring H-U, Merker L, Seewaldt-Becker E, et al. Empagliflozin as Add-on to Metformin Plus Sulfonylurea in Patients With Type 2 Diabetes: A 24-week, randomized, double-blind, placebo-controlled trial. *Diabetes Care*. 2013;36(11):3396-3404.
24. Roden M, Weng J, Eilbracht J, et al. Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Diabetes & Endocrinology*. 2013;1(3):208-219.
25. Rosenstock J, Jelaska A, Wang F, et al. Empagliflozin as Add On to Basal Insulin for 78 Weeks Improves Glycaemic Control with Weight Loss in Insulin-Treated Type 2 Diabetes (T2DM). *Canadian journal of diabetes*. 2013(37S4):S32.
26. Häring H, Merker L, Vedel Christiansen A. Empagliflozin for  $\geq$  76 weeks as add-on to metformin plus sulfonylurea (SU) in patients with type 2 diabetes (T2DM). *Diabetes*. 2014;63(Suppl 1):A280.
27. Häring H-U, Merker L, Seewaldt-Becker E, et al. Empagliflozin as add-on to metformin in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. *Diabetes Care*. 2014;37(6):1650-1659.
28. Kovacs C, Seshiah V, Swallow R, et al. Empagliflozin improves glycaemic and weight control as add-on therapy to pioglitazone or pioglitazone plus metformin in patients with type 2 diabetes: a 24-week, randomized, placebo-controlled trial. *Diabetes, Obesity and Metabolism*. 2014;16(2):147-158.
29. Ridderstråle M, Andersen KR, Zeller C, et al. Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: a 104-week randomised, active-controlled, double-blind, phase 3 trial. *The Lancet Diabetes & Endocrinology*. 2014;2(9):691-700.
30. Rosenstock J, Jelaska A, Frappin G, et al. Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled type 2 diabetes. *Diabetes Care*. 2014;37(7):1815-1823.
31. Vasilakou D, Karagiannis T, Athanasiadou E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. *Annals of internal medicine*. 2013;159(4):262-274.

## Abbreviations

The following abbreviations are used in this review:

DPP-4	– dipeptidyl peptidase-4
SGLT2	– sodium-glucose co-transporter 2 inhibitors
SU	– sulfonylurea
TZD	– thiazolidinediones
T2DM	– type 2 diabetes mellitus