Therapeutic Class Overview
Sodium-glucose co-transporter 2 (SGLT2) Inhibitors

Therapeutic Class

- **Overview/Summary:** Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a class of oral antidiabetic agents approved by the Food and Drug Association (FDA) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.[1-7] The kidneys play a pivotal role in controlling plasma glucose concentration; reabsorbing nearly all plasma glucose in the proximal tubules and preventing glucose excretion in patients with normal glucose-tolerance. Approximately 90% of the filtered renal glucose is done in the early convoluted segment of the proximal tubule and is facilitated by the SGLT2 transporter. The remaining 10% of filtered glucose is reabsorbed in the distal straight segment of the proximal tube by the SGLT1 transporter. In diabetic patients, the SGLT transporter system is often overwhelmed and unable to reabsorb all filtered plasma glucose due to hyperglycemic conditions. Once this threshold capacity is reached and surpassed, excess glucose that is not reabsorbed is excreted into the urine. In addition, a chronic elevated plasma glucose concentration provides the stimulus that ultimately leads to increased SGLT2 expression by the renal proximal tubular cells, resulting in an undesirable increase in renal capacity and threshold to reabsorb filtered glucose in both type 1 and type 2 diabetic patients.[1,2] SGLT2 inhibitors improve glycemic control by producing glucosuria. This is accomplished by inhibiting SGLT2 and increasing urinary glucose excretion. The net effect is an increase excretion of glucose from the body and normalizing plasma glucose levels. At this time, it is unknown if this mechanism of action serves to reduce the kidney's threshold capacity to reabsorb glucose, thus causing glucose excretion at lower plasma concentrations, or if the mechanism of action serves to prevent reabsorption of glucose load at all plasma glucose concentrations. SGLT2 inhibitors also have beneficial nonglycemic effects, such as weight loss observed during clinical trials and small decreases in systolic and diastolic blood pressure.[1,2]

Table 1. Current Medications Available in Therapeutic Class[3-9]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single Agent Products			
Canagliflozin (Invokana®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 100 mg 300 mg	-
Dapagliflozin (Farxiga®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 5 mg 10 mg	-
Empagliflozin (Jardiance®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 10 mg 25 mg	-
Combination Products			
Canagliflozin/ metformin (Invokamet®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes*	Tablet: 50/500 mg 50/1,000 mg 150/500 mg 150/1,000 mg	-
Dapagliflozin/ metformin ER (Xigduo XR®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes†	Tablet: 5/500 mg 5/1000 mg 10/500 mg 10/1000 mg	-
Empagliflozin/ linagliptin (Glyxambi®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes‡	Tablet: 10 mg/5 mg 25 mg/5 mg:	-

Empagliflozin/metformin (Synjardy®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes§	Tablet: 5/500 mg 5/1000 mg 12.5/500 mg 12.5/1000 mg	-

ER=extended-release
*For patients who are not adequately controlled on a regimen containing metformin or canagliflozin or in patients already being treated with both canagliflozin and metformin.
†When treatment with both dapagliflozin and metformin is appropriate.
‡When treatment with both empagliflozin and linagliptin is appropriate.
§When treatment with both empagliflozin and metformin is appropriate.

Evidence-based Medicine

- Each agent has been studied as monotherapy and dual and triple therapy compared to placebo and active controls and combinations of placebo and active controls.
- As monotherapy, patients randomized to canagliflozin 100 or 300 mg daily compared to patients randomized to placebo had a statistically significant improvement in HbA_{1c}. Both doses also resulted in a greater proportion of patients achieving an HbA_{1c} <7.0%, significant reductions in FPG and post prandial glucose (PPG), and in percent body weight reduction compared to placebo. There were also small decreases from baseline in systolic blood pressure relative to placebo (P values not reported).[10]
- As monotherapy in treatment-naïve patients, dapagliflozin was evaluated in two placebo-controlled trials. The first trial included 274 patients randomized to treatment with 2.5, 5 and 10 mg or placebo. At week 24, treatment with dapagliflozin 5 and 10 mg resulted in significant improvements in HbA_{1c} compared to placebo (-0.6, -0.8, -0.9 vs -0.2%, respectively; P<0.05 for 5 and 10 mg comparisons). Change in FPG (-24.1 and -28.8 vs -4.1 mg/dL, respectively) from baseline was also significantly greater in the 5 and 10 mg groups compared to placebo (P<0.05 for both comparisons).[12]
- There have been no clinical efficacy studies conducted with Xigduo XR® (dapagliflozin/metformin) combination tablets. FDA-approval of dapagliflozin/metformin ER was based on previous studies conducted with the bioequivalent single-entity agents.[7] Combination therapy with metformin extended-release in patients who were treatment-naïve led to significantly greater reductions in HbA_{1c} compared to either monotherapy (dapagliflozin or metformin) in the first study (-2.0 vs -1.2 and -1.4%, respectively; P<0.0001) and second study (-2.0 vs -1.5 and -1.4%, respectively; P<0.0001). In the second study, treatment with 10 mg strength (as monotherapy) was also non-inferior to metformin (as monotherapy) for reduction of HbA_{1c}.[14]
- The safety and efficacy of empagliflozin monotherapy was evaluated in a double-blind, placebo-controlled study of patients with type 2 DM (N=986). At week 24, empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in HbA_{1c} (-0.7% and -0.8% vs. 0.1%, respectively; P<0.0001 for both comparisons), FPG (-19 mg/dL and -25 mg/dL vs. 12 mg/dL, respectively; P values not reported) and body weight (-2.8 kg and -3.2 kg vs. -0.4 kg, respectively; P values not reported) compared with placebo.[15]
- There have been no clinical efficacy studies conducted with empagliflozin/metformin combination tablets. FDA-approval of empagliflozin/metformin ER was based on previous studies conducted with the bioequivalent single-entity agents.[9] The safety and efficacy of empagliflozin added to metformin was evaluated in a double-blind, placebo-controlled study of patients with type 2 DM inadequately controlled on at least 1,500 mg of metformin per day (N=637). At week 24, empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in HbA_{1c} (-0.7% and -0.8% vs. 0.1%, respectively; P<0.0001 for both comparisons), FPG (-20 mg/dL and -22 mg/dL vs. 6 mg/dL, respectively; P values not reported) and body weight (-2.5 kg and -2.9 kg vs. -0.5 kg, respectively; P<0.001 for both comparisons) compared with placebo.[24] In addition, the safety and efficacy of empagliflozin was evaluated in an active-control study versus glimepiride (in combination with metformin). The study was a double-blind, active-controlled, non-inferiority design of patients with type 2 DM inadequately controlled on metformin monotherapy (N=1,545). At week 52, empagliflozin 25 mg daily meet the non-inferiority criteria for lowering HbA_{1c} compared to glimepiride (-0.7% vs. -0.7%). There was a greater reduction in FPG and body weight with empagliflozin 25 mg compared to glimepiride;

however the significance was not reported (-19 mg/dL vs. -9 mg/dL and -3.9 kg vs. 2 kg; P values not reported).[25]

- The safety and efficacy of empagliflozin added to linagliptin was evaluated in a 52 week double-blind, active-control, randomized trial. Change from baseline in HbA_{1c} at week 24 was significantly improved in the combination groups compared with the individual component groups (P<0.001).[32] When started as initial therapy, empagliflozin/linagliptin reduced HbA_{1c} from baseline significantly greater when compared with individual linagliptin and empagliflozin 10 mg. Empagliflozin 25 mg/linagliptin 5 mg, however, did not show a statistically significant difference compared with empagliflozin alone (P=0.179).[33]
- Similar results were observed when comparing sodium glucose co-transport 2 agents in combination for the treatment of diabetes mellitus.[17-31]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[34-41]
    - Metformin remains the cornerstone of most antidiabetic treatment regimens.
    - Patients with high glycosylated hemoglobin (HbA_{1c}) will likely require combination or triple therapy in order to achieve glycemic goals.
        - Uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered.
        - The role of sodium-glucose co-transporter 2 (SGLT2) inhibitors are addressed in several available treatment guidelines and are recommended as a potential alternative to metformin in patients who cannot receive that agent or as a part of two- or three-drug regimens in combination with other antidiabetic agents in patients not achieving glycemic goals.[35,38-39]

- Other Key Facts:
    - Canagliflozin is formulated with metformin in a single tablet (Invokamet®). Empagliflozin is formulated with linagliptin in a single tablet (Glyxambi®) and with metformin in a single tablet (Synjardy®). Dapagliflozin is formulated with metformin as a single extended-release tablet (Xigduo XR®).[6-9]
    - All products are dosed once daily, with the exception of canagliflozin/metformin and empagliflozin/metformin, which are dosed twice dialy.[3-9]
    - Other effects observed in trials include weight loss and small decreases in systolic and diastolic blood pressure.
    - Common adverse side effects associated with SGLT2 inhibitor use included increased incidence of female genital mycotic infections, urinary tract infection, and increased urination.

References

1. Abdul-Ghani MA, Norton L, DeFronzo RA. Efficacy and safety of SGLT2 inhibitors in the treatment of type 2 diabetes mellitus. Curr Diab Rep. 2012 Jun;12(3):230-8.
2. Abdul-Ghani MA, Norton L, Defronzo RA. Role of sodium-glucose cotransporter 2 (SGLT 2) inhibitors in the treatment of type 2 diabetes. Endocr Rev. 2011Aug;32(4):515-31.
3. Invokana® [package insert]. Titusville (NJ): Janssen Pharmaceuticals, Inc.; 2014 May.
4. Farxiga® [package insert]. Princeton (NJ): Bristol Myers-Squibb Company; 2015 Mar.
5. Jardiance® [package insert]. Ridgefield (CT): Boehringer Ingelheim Pharmaceuticals, Inc.; 2014 Aug.
6. Invokamet® [package insert]. Titusville (NJ): Janssen Pharmaceuticals, Inc.; 2015 Mar.
7. Xigduo XR® [package insert]. Wilmingtong (DE): AstraZeneca Pharmaceuticals LP; 2014 Oct.
8. Glyzambi® [package insert]. Ridgefield (CT): Boehringer Ingelheim Pharmaceuticals, Inc.; 2015 Jan.
9. Synjardy® [package insert]. Ridgefield (CT): Boehringer Ingelheim Pharmaceuticals, Inc.; 2016 July.
10. Stenlof K, Cefalu WT, Kim KA, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetes Obes Metab. Published online January 24, 2013. doi: 10.1111/dom.12054.
11. Bode B, Stenlof K, Sullivan D, et al. Efficacy and safety of canagliflozin, a sodium glucose cotransporter 2 inhibitor, in older subjects with type 2 diabetes mellitus: a randomized trial. Hosp Pract. Published online before print April 18, 2013. DOI: 10.3810/hp.2013.04.1020.
12. Ferranini E, Ramos SJ, Salsali AM, Tang W, List JF. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise. Diabetes Care. 2010;33(10):2217-24.

13. Bailey CJ, Iqbal N, T'Joen C, List JF. Dapagliflozin monotherapy in drug-naive patients with diabetes: a randomized-controlled trial of low-dose range. Diabetes Obes Metab. Oct 2012;14(10):951-9.
14. Henry RR, Murray AV, Marmolejo MH, Hennicken D, Ptaszynska A, List JF. Dapagliflozin, metformin XR, or both: initial pharmacotherapy for type 2 diabetes, a randomized controlled trial. Int J Clin Pract. May 2012;66(5):446-56.
15. Roden M, Weng J, Eilbracht J, Delafont B, Kim G, Woerle HJ 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. Lancet Diabetes Endocrinol. 2013 Nov;1(3):208-19.
16. Barnett AH, Mithal A, Manassie J, Jones R, Rattunde H, Woerle HJ et al. Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with type 2 diabetes and chronic kidney disease: a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol. 2014 May;2(5):369-84. doi: 10.1016/S2213-8587(13)70208-0.
17. Rosenstock J, Aggarwal N, Polidori D, Zhao Y, Arbit D, Usiskin K, et al. DIA 2001 Study Group. Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes. Diabetes Care. 2012 Jun;35(6):1232-8.
18. Nauck, MA, Del Prato S, Meier JJ. Dapagliflozin vs glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial. Diabetes Care. 2011;34(9):2015-22.
19. Bailey CJ, Gross JL, Pieters A, Bastien A, List JF. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, double-blind, placebo-controlled trial. Lancet. 2010;375:2223-33.
20. Bailey CJ, Gross JL, Hennicken D, Iqbal N, Mansfield TA, List FJ. 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;11:43.
21. Bolinder J, Ljunggren O, Kullberg J, Johansson L, Wilding J, Langkilde AM, et al. Effects of dapagliflozin on body weight, total fat mass and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin. J Clin Endocrinol Metab. 2012 March;97(3):1020-31.
22. Strojek K, Yoon KH, Elze m, Langkilde AM, Parikh S. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. Diabetes Obes Metab. 2011;13:928-38.
23. Rosenstock J, Vico M, Wei L, Salsali A, List JF. 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;35:1473-8.
24. Häring HU, Merker L, Seewaldt-Becker E, Weimer M, Meinicke T, Broedl UC 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 Jun;37(6):1650-9. doi: 10.2337/dc13-2105.
25. Ridderstråle M, Andersen KR, Zeller C, Kim G, Woerle HJ, Broedl UC 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. Lancet Diabetes Endocrinol. 2014 Sep;2(9):691-700. doi: 10.1016/S2213-8587(14)70120-2.
26. Schernthaner G, Gross JL, Rosenstock J, et al. Canagliflozin compared to sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea [published online ahead of print April 5, 2013]. Diabetes Care. http://dx.doi.org/10.2337/dc12-2491 and online supplement available at: http://care.diabetesjournals.org/content/suppl/2013/04/03/dc122491.DC1/DC122491SupplementaryData.pdf.
27. Jabbour A, Hardy E, Sugg J, Parikh S. Dapagliflozin is effective as add-on therapy to sitagliptin with or without metformin: a 24-week, multicenter, randomized, double-blind, placebo-controlled study. Diabetes Care. 2014. Jan 15 [Epub ahead of print].
28. Wilding JP, Woo V, Soler N, et al. Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin. Ann Intern Med. 2012;156:405-415.
29. Häring HU, Merker L, Seewaldt-Becker E, Weimer M, Meinicke T, Woerle HJ 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 Nov;36(11):3396-404.
30. Kovacs CS, Seshiah V, Swallow R, Jones R, Rattunde H, Woerle HJ 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 Obes Metab. 2014 Feb;16(2):147-58. doi: 10.1111/dom.12188.
31. Rosenstock J, Jelaska A, Wang F, et al. Empagliflozin as Add-On to Basal Insulin for 78 Weeks Improves Glycemic Control with Weight Loss in Insulin-Treated Type 2 Diabetes (T2DM). American Diabetes Association (ADA) 73rd Scientific Sessions. Chicago, IL, 2013. Jardiance® formulary dossier. Boehringer Ingelheim, Data on file.
32. DeFronzo RA, Lewin A, Patel S, Liu D, Kaste R, Woerle HJ, Broedl UC. Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin. Diabetes Care. 2015 Mar;38(3):384-93. doi: 10.2337/dc14-2364. Epub 2015 Jan 12.
33. Lewin A, DeFronzo RA, Patel S, Liu D, Kaste R, Woerle HJ, Broedl UC. Initial combination of empagliflozin and linagliptin in subjects with type 2 diabetes. Diabetes Care. 2015 Mar;38(3):394-402. doi: 10.2337/dc14-2365. Epub 2015 Jan 29.
34. The American Diabetes Association. Standards of medical care in diabetes-2016. Diabetes Care. 2016 Jan;39 Suppl 1:S4-5.
35. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach. Update to a position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2015 Jan;38(1):140-49.
36. Qaseem A, Humphrey LL, Sweet DE, Starkey M, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2012;156:218-31.
37. Handelsman Y, Mechanick JI, Blonde L, Grunberger G, Bloomgarden ZT, Bray GA, et al. American Association of Clinical Endocrinologists and American College of Endocrinology – Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan. Endocr Pract. 2015 Apr;21 Suppl 1:1-87.

38. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA et al. Consensus Statement by the American Association Of Clinical Endocrinologists And American College Of Endocrinology On The Comprehensive Type 2 Diabetes Management Algorithm – 2016 Executive Summary. Endocr Pract. 2016;22(1):84-113.
39. National Institute for Health and Clinical Excellence. Type 2 diabetes: the management of type 2 diabetes. [guideline on the Internet]. London: NICE; 2015 Dec [cited 2016 Jun]. Available from: https://www.nice.org.uk/guidance/ng28.
40. Redmon B, Caccamo D, Flavin P, Michels R, Myers C, O'Connor P, Roberts J, Setterlund L, Smith S, Sperl-Hillen J. Institute for Clinical Systems Improvement. Diagnosis and Management of Type 2 Diabetes Mellitus in Adults. Updated July 2014.
41. Copeland, K.C., Silverstein, J., Moore, K.R., Prazar, G.E., Raymer, T., Shiffman, R.N., & et al. (2013). Management of newly diagnosed type 2 diabetes mellitus (T2DM) in children and adolescents. Pediatrics 2013;131(2):364-382.