Therapeutic Class Review
Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

Therapeutic Class

- **Overview/Summary:** A significant advancement in the management of type 2 diabetes has been the development of incretin-based therapies. This novel therapeutic approach is important as type 2 diabetics have been shown to have an impaired incretin response.[1] Currently, there are two classes of incretin-based therapies available: the dipeptidyl pepetidase-4 (DPP-4) inhibitors and the glucagon-like peptide-1 receptor agonists, or incretin mimetics. The DPP-4 inhibitors include alogliptin, linagliptin, saxagliptin, and sitagliptin, which are all available as single-entity agents (alogliptin [Nesina®], linagliptin [Tradjenta®], saxagliptin [Onglyza®], and sitagliptin [Januvia®]) or in fixed-dose combination products (alogliptin/metformin [Kazano®], alogliptin/pioglitazone [Oseni®], linagliptin/empagliflozin [Glyxambi®], linagliptin/metformin [Jentadueto®], saxagliptin/metformin [Kombiglyze ER®], and sitagliptin/metformin [Janumet®, Janumet XR®]).[2-12] The DPP-4 inhibitors are Food and Drug Administration (FDA)-approved as adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes. Single-entity and combination agents containing alogliptin are available for use either as monotherapy or in combination with other antidiabetic agents. The fixed-dose combination products are available for use when treatment with both drug components is appropriate.[2-12]

  The DPP-4 inhibitors reversibly block the DPP-4 enzyme, which is responsible for the rapid degradation of endogenous incretin hormones. These hormones are produced by the gastrointestinal tract in response to meals and are involved in the regulation of insulin. The antidiabetic actions of endogenous incretin hormones include the enhancement of meal-stimulated insulin secretion, decreased glucagon secretion, improvements in β cell function, and slowing of gastric emptying. Through their effect on these hormones, the DPP-4 inhibitors primarily target post-prandial glucose and have also been shown to decrease fasting plasma glucose.[13,14] In general, the DPP-4 inhibitors are associated with a favorable side effect profile and also have a weight neutral effect compared to other antidiabetic agents commonly used in the management of type 2 diabetes. Compared to sulfonylureas, the risk of hypoglycemia associated with the DPP-4 inhibitors is low due to the glucose-dependent nature of incretin hormone activity. In addition, the DPP-4 inhibitors have not been associated with the same increased risk of cardiovascular disease that has been observed with the use of thiazolidinediones (TZDs). The DPP-4 inhibitors improve the function of β cells and although TZDs and metformin treat insulin resistance, these agents do not address the progressive decline in β cell function that is observed in patients with type 2 diabetes.[13-15]

  The DPP-4 inhibitors are available as fixed-dose combination products with metformin. Metformin, a biguanide, improves glucose tolerance in type 2 diabetics by lowering both basal and postprandial plasma glucose. Specifically, the actions of metformin result in decreased hepatic glucose production, decreased intestinal absorption of glucose, and improvement in insulin sensitivity via increased peripheral glucose uptake and utilization.[6-10] Additionally, alogliptin is available in a fixed-dose combination with pioglitazone. Pioglitazone is a TZD, an agonist for peroxisome proliferator-activated receptor-gamma (PPARγ).[11] PPAR receptors are found in adipose, skeletal muscle, and liver tissue and activation of these receptors modulates transcription of insulin response genes that control glucose and lipid metabolism, providing an overall effect of increasing insulin sensitivity in muscle and adipose tissue while inhibiting hepatic gluconeogenesis.[2,11] Linagliptin is available as a fixed-dose combination with empagliflozin (Glyxambi®).[12] Empagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor and improves glycemic control by producing glucosuria. This is accomplished by inhibiting SGLT2 and increasing urinary glucose excretion.[12] The net effect is an increase excretion of glucose from the body and normalization of plasma glucose levels.[12] Overall, the DPP-4 inhibitors are significantly more effective compared to placebo in reducing glycosylated hemoglobin (HbA_{1c}), fasting plasma glucose, and post-prandial glucose, with no major effect on body weight. Combination therapy with a DPP-4 inhibitor and metformin consistently demonstrates improved benefits in glycemic control over monotherapy with either a DPP-4 inhibitor or metformin; limited within class head-to-head trials have been conducted.[16-63,65-68,76,77]

Two meta-analyses revealed that DPP-4 inhibitors are not associated with an increased risk of cardiovascular events or cancer compared to placebo or other antidiabetic agents, respectively.[37,61] However, a recent clinical trial suggested an increased risk of heart-failure with saxagliptin compared to placebo.[38] In April 2016, the FDA added heart failure warnings to the labeling of medications containing saxagliptin and alogliptin.[65]

With regards to the specific DPP-4 inhibitor agents, all single-entity agents are available for once-daily dosing.[2-5] Three fixed-dose combination products contain metformin immediate-release (alogliptin/metformin [Kazano®], linagliptin/metformin [Jentadueto®] and sitagliptin/metformin [Janumet®]) which are available for twice-daily dosing.[6,7,9] One fixed-dose combination product (alogliptin/pioglitazone [Oseni®]) contains pioglitazone and is dosed once daily.[11] Two fixed-dose combination products contain metformin extended-release (ER) (saxagliptin/metformin ER [Kombiglyze XR®] and sitagliptin/metformin ER [Janumet XR®]), and because of the metformin ER component, these products are available for once-daily dosing.[8,10] The fixed-dose combination product containing linagliptin and empagliflozin (Glyxambi®) is also available for once-daily dosing.[12] Single-entity linagliptin is the only agent within the class that does not require renal and hepatic dosing.[3] The fixed-dose combination of alogliptin/pioglitazone [Oseni®] carries a boxed warning regarding the risk of use in patients with congestive heart failure as the TZD component may cause or exacerbate congestive heart failure in some patients.[11] Furthermore, because of the metformin component in certain fixed-dose combination products, caution is recommended with both renal and hepatic dysfunction.[6-10] In addition, these products all have a boxed warning regarding the risk of lactic acidosis due to metformin accumulation.[6-10] Currently, alogliptin, alogliptin/metformin, and alogliptin/pioglitazone are available generically.[2,6,11]

Table 1. Medications Included Within the Therapeutic Class Review[2-12]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Agents			
Alogliptin (Nesina®)	Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 6.25 mg 12.5 mg 25 mg	✔
Linagliptin (Tradjenta®)	Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 5 mg	-
Saxagliptin (Onglyza®)	Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 2.5 mg 5 mg	-
Sitagliptin (Januvia®)	Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 25 mg 50 mg 100 mg	-
Combination Products			
Alogliptin/ metformin (Kazano®)	Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet (alogliptin/ metformin): 12.5/500 mg 12.5/1,000 mg	✔
Alogliptin/ pioglitazone (Oseni®)	Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2	Tablet (alogliptin/ pioglitazone): 12.5/15 mg	✔

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
	diabetes	12.5/30 mg 12.5/45 mg 25/15 mg 25/30 mg 25/45 mg	
Linagliptin/ empagliflozin (Glyxambi®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes*	Tablet (linagliptin/ empagliflozin): 5/10 mg 5/25 mg	-
Linagliptin/ metformin (Jentadueto®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes†	Tablet (linagliptin/ metformin): 2.5/500 mg 2.5/850 mg 2.5/1,000 mg	-
Saxagliptin/ metformin (Kombiglyze XR®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes‡	Tablet (saxagliptin/ metformin ER): 5/500 mg 2.5/1,000 mg 5/1,000 mg	-
Sitagliptin/ metformin (Janumet®, Janumet XR®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes§	Tablet (sitagliptin/ metformin): 50/500 mg 50/1,000 mg Tablet (sitagliptin/ metformin ER): 50/500 mg 50/1,000 mg 100/1,000 mg	-

*When treatment with both linagliptin and empagliflozin is appropriate.
†When treatment with both linagliptin and metformin is appropriate.
‡When treatment with both saxagliptin and metformin extended-release is appropriate.
§When treatment with both sitagliptin and metformin or metformin extended-release is appropriate.
ER=extended-release, XR=extended-release

Evidence-based Medicine

- Clinical trials have demonstrated the safety and efficacy of the dipeptidyl peptidase-4 (DPP-4) inhibitors in the management of type 2 diabetes.[16-63,65-68,76,77] Of note, there have been minimal clinical efficacy or safety trials conducted with any of the DPP-4 inhibitor fixed-dose combination products; bioequivalence of these products with co-administration of the individual drug components has been demonstrated for all tablet strengths.[6-12] Available trials evaluating the fixed-dose combination of sitagliptin/metformin support its efficacy and safety in the management of type 2 diabetes. Specifically, combination therapy was associated with significantly improved glycemic control compared to metformin monotherapy.[57]
- In studies, alogliptin was associated with significant decreases in HbA_{1c} from baseline as monotherapy compared to placebo. In addition, in studies with metformin or pioglitazone combination therapy with alogliptin, significant decreases in HbA_{1c} were observed and more patients reached specific HbA_{1c} goals compared to the monotherapy comparator. As an add-on therapy in patients already being treated with metformin, pioglitazone, metformin/pioglitazone, glipizide or insulin therapy, the additions of alogliptin demonstrated significant improvements in HbA_{1c} from baseline compared to placebo.[16-23]
- Overall, linagliptin is more effective compared to placebo in decreasing HbA_{1c} and fasting plasma glucose (FPG) as monotherapy or as add-on therapy to other antidiabetic agents in type 2 diabetics

not achieving glycemic goals. In addition, more patients achieved glycemic goals (HbA_{1c} <7.0%) with linagliptin compared to placebo.[24-27] Combination therapy with linagliptin and pioglitazone has been shown to be more efficacious in terms of reducing HbA_{1c} compared to pioglitazone monotherapy.[53]
- Similar results were achieved with saxagliptin when compared to placebo.[29-36] In addition, combination therapy with saxagliptin and metformin was "superior" to monotherapy with either agent in observed reductions in HbA_{1c}, FPG, and post-prandial glucose (PPG), and a significantly greater proportion of patients achieved glycemic goals with combination therapy.[55,56]
- Similar to the results of clinical trials evaluating other DPP-4 inhibitors, sitagliptin is consistently more efficacious in improving glycemic control compared to placebo, and combination therapy with sitagliptin and metformin is more efficacious than monotherapy with either agent.[40-51]
- In a single head-to-head trial, saxagliptin demonstrated non-inferiority to sitagliptin in reducing HbA_{1c}. However, a significantly greater proportion of patients achieved an HbA_{1c} ≤6.5% and achieved significant reductions in FPG with sitagliptin compared to saxagliptin.[52] While the beneficial effects of the DPP-4 inhibitors in improving HbA_{1c}, FPG, and PPG compared to placebo are well established, observed improvements in body weight and β cell function with these agents are not consistent.[16-63,64]
- In general, meta-analyses and systematic reviews evaluating incretin-based therapies, including the DPP-4 inhibitors, support the results observed in randomized-controlled trials evaluating these agents.[37,54,62-64,65-68] Two meta-analyses revealed that DPP-4 inhibitors are not associated with an increased risk of cardiovascular events or cancer compared to placebo or other antidiabetic agents, respectively.[37,61]

Key Points within the Medication Class
- According to Current Clinical Guidelines for the management of type 2 diabetes:[69-73,78-80]
    - Metformin remains the cornerstone of most antidiabetic treatment regimens.
    - Additionally, patients with a high HbA_{1c} will likely require combination or triple therapy in order to achieve glycemic goals.
    - At this time, 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 DPP-4 inhibitors are recommended as a potential second-line treatment option to be added in combination with metformin in patients not achieving glycemic goals.
    - Clinical guidelines note a lower rate of hypoglycemia and an established efficacy and safety profile when used in combination with metformin as advantages associated with the DPP-4 inhibitors compared to other classes of antidiabetic agents.
    - Patients who are not appropriate for initial therapy with metformin may be initiated on another oral antidiabetic agent, such as a sulfonylurea/glinide, pioglitazone, or a DPP-4 inhibitor, and in occasional cases where weight loss is seen as an essential aspect of therapy, initial therapy with an incretin mimetic may be useful. Among all current clinical guidelines, preference of one DPP-4 inhibitor over another is not stated.
- Other Key Facts:
    - All single-entity agents are available for once-daily dosing.[2-5]
    - Single-entity linagliptin is the only agent within the class that does not require renal and hepatic dosing.[3]
    - The metformin component in certain fixed-dose combination products requires caution in patients with renal and hepatic dysfunction.[6-10]
    - The DPP-4 inhibitors are associated with low risk of hypoglycemia and is weight neutral when used as monotherapy.[2-12]
    - DPP-4 inhibitors improve the function of β cells in the pancreas.[1-13-15]

References
1. Bagger JI, Knop FK, Lund A, Vestergaard H, Holst JJ, Vilsbøll T. Impaired regulation of the incretin effect in patients with type 2 diabetes. J Clin Endocrinol Metab. 2011 Mar;96(3):737-45.
2. Nesina® [package insert]. Deerfield (IL) Takeda Pharmaceuticals America, Inc.; 2016 May.
3. Tradjenta® [package insert]. Ridgefield (CT): Boehringer Ingelheim Pharmaceuticals, Inc.; 2015 Aug.
4. Onglyza® [package insert]. Wilmington (DE): AstraZeneca Pharmaceuticals; 2016 Apr.
5. Januvia® [package insert]. Whitehouse Station (NJ): Merck & Co., Inc.; 2016 Apr.

6. Kazano® [package insert]. Deerfield (IL) Takeda Pharmaceuticals America, Inc.; 2016 May.
7. Jentadueto® [package insert]. Ridgefield (CT) and Indianapolis (IN): Boehringer Ingelheim Pharmaceuticals, Inc. and Eli Lilly and Company; 2015 Aug.
8. Kombiglyze XR® [package insert]. Wilmington (DE): AstraZeneca Pharmaceuticals; 2016 Apr.
9. Janumet® [package insert]. Whitehouse Station (NJ): Merck & Co., Inc.; 2016 Apr.
10. Janumet XR® [package insert]. Whitehouse Station (NJ): Merck & Co., Inc.; 2016 Apr.
11. Oseni® [package insert]. Deerfield (IL) Takeda Pharmaceuticals America, Inc.; 2016 Apr.
12. Glyxambi® [package insert]. Ridgefield (CT) and Indianapolis (IN): Boehringer Ingelheim Pharmaceuticals, Inc. and Eli Lilly and Company; 2015 Dec.
13. Miller SA, St. Onge EL, Taylor JR. DPP-IV inhibitors: A review of sitagliptin, vildagliptin, alogliptin, and saxagliptin. Formulary. 2008;43:122-34.
14. Deacon CF, Holst JJ. Saxagliptin: a new dipeptidyl peptidase-4 inhibitor for the treatment of type 2 diabetes. Adv Ther. 2009;26(5):488-99.
15. Barnett AH. Linagliptin: a novel dipeptidyl peptidase 4 inhibitor with a unique place in therapy. Adv Ther. 2011;28(6):447-59.
16. DeFronzo RA, Fleck PR, Wilson CA, Mekki Q; Alogliptin Study 010 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin in patients with type 2 diabetes and inadequate glycemic control: a randomized, double-blind, placebo-controlled study. Diabetes Care. 2008 Dec;31(12):2315-7.
17. Rosenstock J, Inzucchi SE, Seufert J, Fleck PR, Wilson CA, Mekki Q. Initial combination therapy with alogliptin and pioglitazone in drug-naïve patients with type 2 diabetes. Diabetes Care. 2010 Nov;33(11):2406-8.
18. Nauck MA, Ellis GC, Fleck PR, Wilson CA, Mekki Q; Alogliptin Study 008 Group. Efficacy and safety of adding the dipeptidyl peptidase-4 inhibitor alogliptin to metformin therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy: a multicentre, randomised, double-blind, placebo-controlled study. Int J Clin Pract. 2009 Jan;63(1):46-55.
19. DeFronzo RA, Burant CF, Fleck P, Wilson C, Mekki Q, Pratley RE. Efficacy and tolerability of the DPP-4 inhibitor alogliptin combined with pioglitazone, in metformin-treated patients with type 2 diabetes. J Clin Endocrinol Metab. 2012 May;97(5):1615-22.
20. Pratley RE, Reusch JE, Fleck PR, Wilson CA, Mekki Q; Alogliptin Study 009 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin added to pioglitazone in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled study. Curr Med Res Opin. 2009 Oct;25(10):2361-71.
21. Bosi E, Ellis GC, Wilson CA, Fleck PR. Alogliptin as a third oral antidiabetic drug in patients with type 2 diabetes and inadequate glycaemic control on metformin and pioglitazone: a 52-week, randomized, double-blind, active-controlled, parallel-group study. Diabetes Obes Metab. 2011 Dec;13(12):1088-96.
22. Pratley RE, Kipnes MS, Fleck PR, Wilson C, Mekki Q; Alogliptin Study 007 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin in patients with type 2 diabetes inadequately controlled by glyburide monotherapy. Diabetes Obes Metab. 2009 Feb;11(2):167-76.
23. Rosenstock J, Rendell MS, Gross JL, Fleck PR, Wilson CA, Mekki Q. Alogliptin added to insulin therapy in patients with type 2 diabetes reduces HbA(1C) without causing weight gain or increased hypoglycaemia. Diabetes Obes Metab. 2009 Dec;11(12):1145-52.
24. Del Prato S, Barnett AH, Huisman H, Neubacher D, Woerle HJ, Dugi KA. Effect of linagliptin monotherapy on glycemic control and markers of β-cell function in patients with inadequately controlled type 2 diabetes: a randomized controlled trial. Diabetes Obes Metab. 2011;13:258-67.
25. Taskinen MR, Rosenstock J, Tamminen I, Kubiak R, Patel S, Dugi KA, et al. Safety and efficacy of linagliptin as add-on therapy to metformin in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled study. Diabetes Obes Metab. 2011;13:65-74.
26. Owens DR, Swallow R, Dugi KA, Woerle HJ. Efficacy and safety of linagliptin in persons with type 2 diabetes inadequately controlled by a combination of metformin and sulphonylurea: a 24-week randomized study. Diabet Med. 2011;28:1352-61.
27. Forst T, Uhlig-Laske B, Ring A, Graefe-Mody U, Friedrich C, Herbach K, et al. Linagliptin (BI 1356), a potent and selective DPP-4 inhibitor, is safe and efficacious in combination with metformin in patients with inadequately controlled type 2 diabetes. Diabet Med. 2010;27:1409-19.
28. Haak T, Meinicke T, Jones R, Weber S, von Eynatten M, Woerle HJ. Initial combination of linagliptin and metformin improves glycemic control in type 2 diabetes: a randomized, double-blind, placebo-controlled study. Diabetes Obes Metab. 2012;14:565-74.
29. Hollander P, Li J, Allen E, Chen R; CV181-013 Investigators. Saxagliptin added to a thiazolidinedione improves glycemic control in patients with type 2 diabetes and inadequate control on thiazolidinedione alone. J Clin Endocrinol Metab. 2009 Dec;94(12):4810-9.
30. Chacra AR, Tan GH, Apanovitch A, Ravichandran S, List J, Chen R. Saxagliptin added to submaximal dose of sulfonylurea improves glycemic control compared to up titration of sulfonylurea in patients with type 2 diabetes: a randomized controlled trial. Int J Clin Prac. 2009;63(9):1395-406.
31. Chacra AR, Tan GH, Ravichandran S, List J, Chen R; CV181040 Investigators. Safety and efficacy of saxagliptin in combination with submaximal sulphonylurea vs up-titrated sulphonylurea over 76 weeks. Diab Vasc Dis Res. 2011 Apr;8(2):150-9.
32. Rosenstock J, Aquilar-Salinas C, Klien E, Nepal S, List J, Chen R. Effect of saxagliptin monotherapy in treatment-naïve patients with type 2 diabetes [abstract]. Curr Med Res Opin. 2009 Oct;25(10):2401-11.
33. DeFronzo RA, Hissa MN, Garber AJ, Luiz Gross J, Yuyan Duan R, Ravichandran S, et al; Saxagliptin 014 Study Group. The efficacy and safety of saxagliptin when added to metformin therapy in patients with inadequately controlled type 2 diabetes with metformin alone. Diabetes Care. 2009;32(9):1649-55.
34. Stenlöf K, Raz I, Neutel J, Ravichandran S, Berglind N, Chen R. Saxagliptin and metformin XR combination therapy provides glycemic control over 24 hours in patients with T2DM inadequately controlled with metformin. Curr Med Res Opin. 2010 Oct;26(10):2355-63.

35. Barnett AH, Charbonnel B, Donovan M, Fleming D, Chen R. Effect of saxagliptin as add-on therapy in patients with poorly controlled type 2 diabetes on insulin alone or insulin combined with metformin. Curr Med Res Opin. 2012 Apr;28(4):513-23.
36. Rosenstock J, Sankoh S, List JF. Glucose-lowering activity of the dipeptidyl peptidase-4 inhibitor saxagliptin in drug-naive patients with type 2 diabetes. Diabetes Obes Metab. 2008;10(5):376-86.
37. Frederich R, Alexander JH, Fiedorek FT, Donovan M, Berglind N, Harris S, et al. A systematic assessment of cardiovascular outcomes in the saxagliptin drug development program for type 2 diabetes. Postgrad Med. 2010 May;122(3):16-27.
38. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013 Oct 3;369(14):1317-26. doi: 10.1056/NEJMoa1307684.
39. Harashima SI, Ogura M, Tanaka D, Fukushima T, Wang Y, Koizumi T, et al. Sitagliptin add-on to low dosage sulphonylureas: efficacy and safety of combination therapy on glycemic control and insulin secretion capacity in type 2 diabetes. Int J Clin Pract. 2012 May;66(5):465-76.
40. Brazg R, Xu L, Dalla Man C, Cobelli C, Thomas K, Stein PP. Effect of adding sitagliptin, a dipeptidyl peptidase-4 inhibitor, to metformin on 24-h glycemic control and beta-cell function in patients with type 2 diabetes. Diabetes Obes Metab. 2007 Mar;9(2):186-93.
41. Nonaka K, Kakikawa T, Sato A, Okuyama K, Fujimoto G, Kato N, et al. Efficacy and safety of sitagliptin monotherapy in Japanese patients with type 2 diabetes. Diabetes Res Clin Pract. Diabetes Res Clin Pract. 2008 Feb;79(2):291-8.
42. Raz I, Chen Y, Wu M, Hussain S, Kaufman KD, Amatruda JM, et al. Efficacy and safety of sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes. Cur Med Res Opin. 2008;24(2):537-50.
43. Charbonnel B, Karasik A, Liu J, Wu M, Meininger G; Sitagliptin Study 020 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. Diabetes Care. 2006 Dec;29(12):2638-43.
44. Rosenstock J, Brazg R, Andryuk PJ, Lu K, Stein P; Sitagliptin Study 019 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing pioglitazone therapy in patients with type 2 diabetes: a 24-week, multicenter, randomized double-blind, placebo-controlled, parallel-group study. Clin Ther. 2006 Oct;28(10):1556-68.
45. Hermansen K, Kipnes M, Luo E, Fanurik D, Khatami H, Stein P; Sitagliptin Study 035 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin. Diabetes Obes Metab. 2007 Sep;9(5):733-45.
46. Raz I, Hanefeld M, Xu L, Caria C, Williams-Herman D, Khatami H; Sitagliptin Study 023 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy in patients with type 2 diabetes mellitus. Diabetologia. 2006 Nov;49:2564-71.
47. Aschner P, Kipnes MS, Lunceford JK, Sanchez M, Mickel C, Williams-Herman DE; Sitagliptin Study 021 Group. Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. Diabetes Care. 2006 Dec;29(12):2632-7.
48. Hanefeld M, Herman GA, Wu M, Mickel C, Sanchez M, Stein PP. Once-daily sitagliptin, a dipeptidyl peptidase-4 inhibitor, for the treatment of patients with type 2 diabetes. Curr Med Res Opin. 2007 Jun;23(6):1329-39.
49. Scott R, Wu M, Sanchez M, Stein P. Efficacy and tolerability of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy over 12 weeks in patients with type 2 diabetes. Int J Clin Pract. 2007 Jan;61(1):171-80.
50. Goldstein BJ, Feinglos MN, Lunceford JK, Johnson J, Williams-Herman DE Sitagliptin 036 Study Group. Effect of initial combination therapy with sitagliptin, a dipeptidyl peptidase-4 inhibitor, and metformin on glycemic control in patients with type 2 diabetes. Diabetes Care. 2007 Aug;30(8):1979-87.
51. Scott R, Loeys T, Davies MJ, Engel SS; Sitagliptin Study 801 Group. Efficacy and safety of sitagliptin when added to ongoing metformin therapy in patients with type 2 diabetes. Diabetes Obes Metab. 2008 Sep;10(10):959-69.
52. Scheen AJ, Charpentier G, Ostgren CJ, Hellqvist A, Gause-Nilsson I. Efficacy and safety of saxagliptin in combination with metformin compared to sitagliptin in combination with metformin in adult patients with type 2 diabetes mellitus. Diabetes Metab Res Rev. 2010 Oct;26(7):540-9.
53. Esposito K, Cozzolino D, Bellastella G, Maiorino MI, Chiodini P, Ceriello A, et al. Dipeptidyl peptidase-4 inhibitors and HbA1c target of <7% in type 2 diabetes: meta-analysis of randomized controlled trials. Diabetes Obes Metab. 2011 Jul;13(7):594-603.
54. Gomis R, Espadero RM, Jones R, Woerle HJ, Dugi KA. Efficacy and safety of initial combination therapy with linagliptin and pioglitazone in patients with inadequately controlled type 2 diabetes: a randomized, double-blind, placebo-controlled study. Diabetes Obes Metab. 2011;13:653-61.
55. Jadzinsky M, Pfutzner A, Paz-Pacheco E, Xu Z, Allen E, Chen R; CV181-039 Investigators. Saxagliptin given in combination with metformin as initial therapy improves glycemic control in patients with type 2 diabetes compared to either monotherapy: a randomized controlled trial. Diabetes Obes Metab. 2009;11(6):611-22.
56. Pfützner A, Paz-Pacheco E, Allen E, Frederich R, Chen R; CV181039 Investigators. Initial combination therapy with saxagliptin and metformin provides sustained glycemic control and is well tolerated for up to 76 weeks. Diabetes Obes Metab. 2011 Jun;13(6):567-76.
57. Reasner C, Olansky L, Seck TL, Williams-Herman DE, Terranella L, et al. The effect of initial therapy with the fixed-dose combination of sitagliptin and metformin compared to metformin monotherapy in patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2011 Jul;13(7):644-52.
58. Bergenstal RM, Wysham C, MacConell L, Malloy J, Walsh B, Yan P, et al. Efficacy and safety of exenatide once weekly vs sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomized trial. Lancet. 2010;376:431-9.
59. Alba M, Ahrén B, Inzucchi SE, Guan Y, Mallick M, Xu L et al. Sitagliptin and pioglitazone provide complementary effects on postprandial glucose and pancreatic islet cell function. Diabetes Obes Metab. 2013 Dec;15(12):1101-10. doi: 10.1111/dom.12145.
60. Russell-Jones D, Cuddihy RM, Hanefeld M, Kumar A, Gonzolez JG, Chan M, et al. Efficacy and safety of exenatide once weekly vs metformin, pioglitazone, and sitagliptin used as monotherapy in drug-naive patients with type 2 diabetes (DURATION-4). Diabetes Care. 2012;35:252-8.

61. Monami M, Dicembrini I, Martelli D, Mannucci E. Safety of dipeptidyl peptidase-4 inhibitors: a meta-analysis of randomized clinical trials. Curr Med Res Opin 2011;27 Suppl 3:57-64.
62. Fakhoury WKH, LeReun C, Wright D. A meta-analysis of placebo-controlled clinical trials assessing the efficacy and safety of incretin-based medications in patients with type 2 diabetes. Pharmacology. 2010;86(1):44-57.
63. Richter B, Bandeira-Echtler E, Bergerhoff K, Lerch CL. Dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD006739.
64. FDA Drug Safety Communication: DA adds warnings about heart failure risk to labels of type 2 diabetes medicines containing saxagliptin and alogliptin [press release on the Internet]. Rockville (MD): Food and Drug Administration (US): 2016 Apr 5 [cited 2016 Jun 16]. Available from: http://www.fda.gov/Drugs/DrugSafety/ucm486096.htm
65. Pinelli NR, Hurren KM. Efficacy and safety of long-acting glucagon-like peptide-1 receptor agonists compared to exenatide twice daily and sitagliptin in type 2 diabetes mellitus: a systematic review and meta-analysis. Ann Pharmacother. 2011;45:850-60.
66. Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes. JAMA. 2007;298(2):194-206.
67. Shyangdan DS, Royle P, Clar C, Sharma P, Waugh N, Snaith A. Glucagon-like peptide analogues for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews 2011, Issue 10. Art. No.: CD006423. DOI: 10.1002/14651858.CD006423.pub2.
68. Schwarz B, Gouveia M, Chen J, Nocea G, Jameson K, Cook J, Krishnarajah G, Alemao E, Yin D, Sintonen H. Cost-effectiveness of sitagliptin-based treatment regimens in European patients with type 2 diabetes and hemoglobin A1c above target on metformin monotherapy. Diabetes Obes Metab. 2008 Jun;10(Suppl 1):S43-55.
69. The American Diabetes Association. Standards of medical care in diabetes-2016. Diabetes Care. 2016 Jan;39 Suppl 1:S4-5.
70. 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.
71. 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.
72. 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.
73. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA et al. American Association of Clinical Endocrinologists Comprehensive Diabetes Management Algorithm 2013. Endocr Pract. 2013;19(2):327-36.
74. Drug Facts and Comparisons [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2013 [cited 2013 Jun]. Available from: http://online.factsandcomparisons.com.
75. Micromedex® Healthcare Series [intranet database]. Version 5.1. Greenwood Village, Colo: Thomson Healthcare. Cited 2013 Jun]. Available from: http://www.thomsonhc.com/.
76. 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.
77. 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.
78. 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.
79. 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.
80. 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.