OPTUMRx

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

INTRODUCTION

- In the United States (US), diabetes mellitus affects more than 30 million people and is the 7th leading cause of death (*Centers for Disease Control and Prevention [CDC] 2018*).
- Type 2 diabetes mellitus (T2DM) is the most common form of diabetes and is characterized by elevated fasting and postprandial glucose concentrations *(American Diabetes Association [ADA] 2019[a])*. It is a chronic illness that requires continuing medical care and ongoing patient self-management education and support to prevent acute complications and to reduce the risk of long-term complications *(ADA 2019[b])*.
  - Complications of T2DM include hypertension, heart disease, stroke, vision loss, nephropathy, and neuropathy *(ADA 2019[a])*.
- In addition to dietary and lifestyle management, T2DM can be treated with insulin, one or more oral medications, or a combination of both. Many patients with T2DM will require combination therapy *(Garber et al 2019)*.
- Classes of oral medications for the management of blood glucose levels in patients with T2DM focus on increasing insulin secretion, increasing insulin responsiveness, or both, decreasing the rate of carbohydrate absorption, decreasing the rate of hepatic glucose production, decreasing the rate of glucagon secretion, and blocking glucose reabsorption by the kidney *(Garber et al 2019)*.
- Pharmacologic options for T2DM include sulfonylureas (SFUs), biguanides, thiazolidinediones (TZDs), meglitinides, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogs, amylinomimetics, sodium-glucose cotransporter 2 (SGLT2) inhibitors, combination products, and insulin *(Garber et al 2019)*.
- The DPP-4 inhibitors or gliptins (alogliptin, linagliptin, saxagliptin, sitagliptin) are indicated as adjuncts to diet and exercise to improve glycemic control in adults with T2DM. All of the DPP-4 inhibitors are available as combination products with metformin hydrochloride (HCl) and/or extended-release metformin HCl *(Drugs@FDA 2019)*.
  - Alogliptin is also approved as a combination product with pioglitazone (a thiazolidinedione [TZD]).
  - Linagliptin is also approved as a combination product with empagliflozin (an SGLT2 inhibitor).
  - Saxagliptin is also approved as a combination product with dapagliflozin (an SGLT2 inhibitor).
  - Sitagliptin is also approved as a combination product with ertugliflozin (an SGLT2 inhibitor).
- The activity of the DPP-4 inhibitors is based on inhibition of the DPP-4 enzyme that mediates physiological degradation of the incretin hormones, glucagon-like peptide 1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP) *(Davis 2014)*. GLP-1 and GIP are secreted by specialized mucosal intestinal cells in response to a meal, promoting insulin biosynthesis and release, as well as other aspects of pancreatic beta cell function in a glucose-dependent manner which circumvents hypoglycemia *(Davis 2014)*. GLP-1 inhibits inappropriate glucagon secretion, delays gastric emptying and, at higher concentrations, suppresses appetite *(Davis 2014)*.
- DPP-4 inhibitors have modest glycated hemoglobin (HbA1c)-lowering properties, are weight neutral, and are associated with a low risk of hypoglycemia *(American Diabetes Association [ADA] 2018, Garber et al 2018)*. DPP-4 inhibitors are not considered as initial therapy for the majority of patients with T2DM *(ADA 2018)*. Indicated as adjuncts to diet and exercise, DPP-4 inhibitors are generally considered after patients have tried/failed metformin (ie, glycemic targets have not been achieved after 3 months at maximum tolerated doses and thus, a DPP-4 can be considered as add-on therapy) or when patients are otherwise intolerant or unable to take metformin, in which case, a DPP-4 inhibitor may be considered as monotherapy *(ADA 2018, Deacon et al 2016, Garber et al 2018, Dungan 2017)*.
- The choice of antidiabetic therapy should be individualized based upon patient specific factors such as comorbidities, the risk of hypoglycemia, and potential adverse effects *(ADA 2018)*.
- Medispan Class: Antidiabetics, Dipeptidyl -4 (DPP-4) inhibitors

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Alogliptin-containing products*	
Nesina (alogliptin)	✔
Kazano (alogliptin/metformin HCl)	✔

Drug	Generic Availability
Oseni (alogliptin/pioglitazone)	✔
Linagliptin-containing products	
Tradjenta (linagliptin)	-
Glyxambi (linagliptin/empagliflozin)	-
Jentadueto (linagliptin/metformin HCl)	-
Jentadueto XR (linagliptin/metformin HCl extended-release)	-
Saxagliptin-containing products	
Onglyza (saxagliptin)	-
Kombiglyze XR (saxagliptin/metformin HCl extended-release)	-
Qtern (saxagliptin/dapagliflozin)	-
Sitagliptin-containing products	
Januvia (sitagliptin)	-
Janumet (sitagliptin/metformin HCl)	-
Janumet XR (sitagliptin/metformin HCl extended-release)	-
Steglujan (sitagliptin/ertugliflozin)	-

*Alogliptin-containing products have been made available by two different manufacturers. Takeda Pharmaceuticals makes brand Nesina, Kazano, and Oseni. Perrigo Pharmaceuticals markets the authorized generics alogliptin, alogliptin/metformin, and alogliptin/pioglitazone *(Perrigo Pharmaceuticals Web site)*.

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. Food and Drug Administration (FDA) Approved Indications: Alogliptin-containing products

Indication	Nesina (alogliptin)*	Kazano (alogliptin/metformin HCl)*	Oseni (alogliptin/pioglitazone)*
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM	✔		
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM in multiple clinical settings when treatment with both alogliptin and metformin is appropriate		✔	
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM in multiple clinical settings when treatment with both alogliptin and pioglitazone is appropriate			✔

* Limitation of use: Should not be used for the treatment of type 1 diabetes or diabetic ketoacidosis, as it would not be effective in those settings.

(Prescribing information: Kazano 2017, Nesina 2016, Oseni 2017)

Table 3. Food and Drug Administration Approved Indications: Linagliptin-containing products

Indication	Tradjenta (linagliptin)*†	Glyxambi (linagliptin/ empagliflozin)*†	Jentadueto (linagliptin/ metformin HCl)*†	Jentadueto XR (linagliptin/ metformin HCl extended-release)*†
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM	✔			
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both linagliptin and empagliflozin is		✔		

Indication	Tradjenta (linagliptin)*†	Glyxambi (linagliptin/ empagliflozin)*†	Jentadueto (linagliptin/ metformin HCl)*†	Jentadueto XR (linagliptin/ metformin HCl extended-release)*†
appropriate Empagliflozin is indicated to reduce the risk of cardiovascular (CV) death in adults with T2DM and established CV disease; however, the effectiveness of Glyxambi on reducing the risk of CV death in adults with T2DM and CV disease has not been established				
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both linagliptin and metformin is appropriate			✔	✔

* Limitation of use: Should not be used for the treatment of type 1 diabetes or diabetic ketoacidosis, as it would not be effective in those settings.

† Limitation of use: Has not been studied in patients with a history of pancreatitis.

(Prescribing information: Glyxambi 2018, Jentadueto 2017, Jentadueto XR 2017, Tradjenta 2017)

Table 4. Food and Drug Administration Approved Indications: Saxagliptin-containing products

Indication	Onglyza (saxagliptin)*	Kombiglyze XR (saxagliptin/ metformin HCl extended-release)*	Qtern (saxagliptin/dapagliflozin)*†
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM	✔		
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both saxagliptin and metformin is appropriate		✔	
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM who have inadequate control with dapagliflozin or who are already treated with dapagliflozin and saxagliptin			✔

***** Limitation of use: Should not be used for the treatment of type 1 diabetes or diabetic ketoacidosis, as it would not be effective in those settings.

† Limitation of use: Should only be used in patients who can tolerate 10 mg dapagliflozin.

(Prescribing information: Kombiglyze XR 2017, Onglyza 2017, Qtern 2018)

Table 5. Food and Drug Administration Approved Indications: Sitagliptin-containing products

Indication	Januvia (sitagliptin)*†	Janumet (sitagliptin/ metformin HCl)*†	Janumet XR (sitagliptin/ metformin HCl extended-release)*†	Steglujan (sitagliptin/ ertugliflozin)*†
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM	✔			
As an adjunct to diet and exercise to improve glycemic control in adults with		✔		

Indication	Januvia (sitagliptin)*†	Janumet (sitagliptin/ metformin HCl)*†	Janumet XR (sitagliptin/ metformin HCl extended-release)*†	Steglujan (sitagliptin/ ertugliflozin)*†
T2DM when treatment with both sitagliptin and metformin is appropriate				
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both sitagliptin and metformin extended-release is appropriate			✔	
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both sitagliptin and ertugliflozin is appropriate				✔

***** Limitation of use: Should not be used for the treatment of type 1 diabetes or diabetic ketoacidosis, as it would not be effective in those settings.

† Limitation of use: Has not been studied in patients with a history of pancreatitis.

(Prescribing information: Janumet 2018, Janumet XR 2018, Januvia 2018, Steglujan 2018)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Alogliptin-containing products

- In the following 10 pivotal trials described in the Nesina prescribing information (2016) and published as cited, alogliptin has been shown to have activity for improving glucose control when:
  - used as monotherapy vs placebo *(DeFronzo et al 2008)*
  - used as initial combination therapy with metformin vs placebo or alogliptin or metformin monotherapy *(Pratley et al 2014)*
  - used as add-on therapy to metformin vs placebo + metformin *(Nauck et al 2009)*
  - used as combination add-on therapy with pioglitazone to metformin vs placebo or alogliptin or pioglitazone monotherapy *(DeFronzo et al 2012)*
  - used as add-on therapy to pioglitazone vs placebo + pioglitazone *(Pratley et al 2009[a])*
  - used as add-on therapy to pioglitazone vs alogliptin or pioglitazone monotherapy *(Rosenstock et al 2010)*
  - used as add-on combination therapy with pioglitazone and metformin vs placebo + pioglitazone and metformin *(Bosi et al 2011)*
  - used as add-on therapy to glyburide (an SFU) vs placebo + glyburide *(Pratley et al 2009[b])*
  - used as add-on therapy to insulin +/- metformin vs placebo + insulin +/- metformin *(Rosenstock et al 2009[a])*
  - used as monotherapy vs glipizide *(Rosenstock et al 2013[b])*
- There have been no clinical efficacy studies conducted with Kazano, the alogliptin/metformin combination product. However, bioequivalence of Kazano with co-administered alogliptin and metformin tablets was demonstrated, and the efficacy of the combination of alogliptin and metformin has been demonstrated in three Phase 3 efficacy studies *(Bosi et al 2011, Nauck et al 2009, Pratley et al 2014)*.
- There have been no clinical efficacy studies conducted with Oseni, the alogliptin/pioglitazone combination product. However, bioequivalence of Oseni with co-administered alogliptin and pioglitazone tablets was demonstrated and the efficacy of the combination of alogliptin and pioglitazone has been demonstrated in four Phase 3 efficacy studies *(Bosi et al 2011, DeFronzo et al 2012, Pratley et al 2009[a], Rosenstock et al 2010)*.

- **CV outcomes** *(White et al 2011, White et al 2013, Zannad et al 2015)*
  - Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) was a Phase 3, double-blind (DB), placebo-controlled (PC), multi-center (MC), randomized controlled trial (RCT) [N = 5380] conducted to determine whether alogliptin was noninferior to placebo with respect to major CV events in patients with T2DM who

were at very high CV risk. The primary endpoint was a composite of death from CV causes, nonfatal myocardial infarction (MI), or nonfatal stroke.
  - A primary endpoint event occurred in 305 patients assigned to alogliptin (11.3%) and in 316 patients assigned to placebo (11.8%) (hazard ratio [HR] = 0.96, upper boundary of the one-sided repeated confidence interval [CI]: 1.16; $p < 0.001$ for noninferiority).
  - Based on the intent-to-treat (ITT) population, more patients in the alogliptin group (106/2701 [rate of 2.6 per 100 patient-years]) than in the placebo group (89/2679 [rate of 2.2 per 100 patient-years]) were hospitalized for heart failure (HF) (3.9% vs 3.3%, HR = 1.19; 95% CI, 0.90 to 1.58; p = 0.220); however, this result was not statistically significant, and the association between alogliptin and hospitalization for HF remains inconclusive *(FDA Drug Safety Communication 2016, FDA Endocrinologic and Metabolic Drugs Advisory Committee 2015, Zannad et al 2015)*.

Linagliptin-containing products

- In the following 10 pivotal trials described in the Tradjenta prescribing information (2017) and published as cited, linagliptin has been shown to have activity for improving glucose control when:
  - used as monotherapy vs placebo *(Barnett et al 2012[b], Del Prato et al 2011)*
  - used as add-on therapy to metformin vs placebo + metformin *(Taskinen et al 2011)*
  - used as initial combination therapy with metformin vs placebo or linagliptin or metformin monotherapy *(Haak et al 2012)*
  - used with metformin vs glimepiride + metformin *(Gallwitz et al 2012)*
  - used as add-on combination therapy with pioglitazone vs placebo + pioglitazone *(Gomis et al 2011)*
  - used as add-on combination therapy with an SFU vs placebo + an SFU *(Lewin et al 2012)*
  - used as add-on combination therapy with metformin and an SFU vs placebo + metformin + an SFU *(Owens et al 2011)*
  - used as add-on combination therapy with insulin vs placebo + insulin *(Yki-Järvinen et al 2013)*
  - used in patients with severe renal impairment vs placebo *(McGill et al 2014)*
- There have been no clinical efficacy studies conducted with Jentadueto, the linagliptin/metformin combination product; bioequivalence of Jentadueto to linagliptin and metformin co-administered as individual tablets was demonstrated in healthy subjects. The labeling of Jentadueto includes the results of some of the aforementioned studies *(Gallwitz et al 2012, Haak et al 2012, McGill et al 2014, Owens et al 2011, Ross et al 2015, Taskinen et al 2011, Yki-Järvinen et al 2013)*, as well as confirmatory results from a 24-week, DB, RCT designed to assess the efficacy of linagliptin in combination with metformin vs linagliptin monotherapy + placebo *(Ross et al 2015)*.
- The safety and efficacy of Jentadueto XR, the linagliptin/metformin ER combination product, have been established on the basis of the aforementioned adequate and well-controlled studies of linagliptin and metformin co-administered in patients with T2DM inadequately controlled on diet and exercise and in combination with an SFU *(Gallwitz et al 2012, Haak et al 2012, Owens et al 2011, Ross et al 2015, Taskinen et al 2011)*. No new studies were conducted with Jentadueto XR.
- Glyxambi, the linagliptin/empagliflozin combination product, was shown to have activity in improving glucose control when used as add-on combination therapy with metformin *(DeFronzo et al 2015, Lewin et al 2015)*.
- **CV outcomes** *(Rosenstock et al 2015[a])*
  - A pooled safety analysis of all DB, RCTs ≥ 12 weeks' duration (19 trials; N = 9459 subjects) found that linagliptin was not associated with an increase in CV risk, compared with a pooled comparator group of placebo, glimepiride, or voglibose (not available in the United States), in patients with T2DM, irrespective of background therapy.
    - Overall, 420 patients with adverse events (AEs) were identified from the pre-specified list of trigger events. A total of 60 (1.0%) primary components of 4-point major adverse cardiac events (4P-MACE) (ie, CV death, stroke, MI, and hospitalization for unstable angina) were reported in the linagliptin group and 62 (1.7%) in the comparator group. The incidence rate of 4P-MACE was 13.4 events per 1000 patient-years for linagliptin-treated patients compared with 18.9 in the active comparator group with a Cox regression HR indicating no significant difference between the 2 treatment groups (HR = 0.78; 95% CI, 0.55 to 1.12).
    - In the placebo cohort of the overall group (ie, 18 of the 19 trials; n = 7746), 4P-MACE incidence rates were 14.9 per 1000 patient-years for linagliptin (43 events) and 16.4 for total comparators (29 events), yielding an overall HR = 1.09 (95% CI: 0.68 to 1.75).
    - In the placebo cohort, there was no signal for an increased risk of either all-cause or CV mortality with linagliptin therapy. All-cause mortality for linagliptin (2538 patient-years exposure) vs placebo (1608 patient-years exposure)

was reported for 13 vs 11 patients, respectively (HR = 0.81; 95% CI, 0.36 to 1.81). For CV mortality with linagliptin (2538 patient-years exposure) vs placebo (1608 patient-years exposure), 8 vs 6 deaths were reported, respectively (HR = 0.88; 95% CI, 0.30 to 2.55).
    - For hospitalization for congestive heart failure (CHF), a small number of patients reported events (n = 21), and the overall risk estimate was similar for linagliptin (12 events; 2039 patients) and the total comparator group (9 events, 1275 patients), with an HR = 1.04 (95% CI: 0.43 to 2.47).
  - CAROLINA, the CARdiovascular Outcome trial of LINAgliptin vs glimepiride in T2DM, is an ongoing, randomized trial in subjects with early T2DM and increased CV risk or established complications that will determine the long-term CV impact of linagliptin vs the SFU glimepiride *(Marx et al 2015, Rosenstock et al 2013[a])*. Started in 2010 with 6041 randomized patients, CAROLINA is the first head-to-head CV outcome trial of a DPP-4 inhibitor vs an active comparator that is sufficiently powered to demonstrate potential differences in CV events between treatment groups *(Rosenstock et al 2015[a])*. The estimated study completion date is September 2018 *(Rosenstock et al 2015[a])*.
  - CARdiovascular Safety & Clinical outcoME with LINAgliptin (CARMELINA) was a DB, PC, MC, RCT (N = 6979) that evaluated CV and renal outcomes with linagliptin in patients with T2DM and high CV and renal risk over a median follow-up of 2.2 years. For the primary outcome of 3-point MACE (composite of CV death, nonfatal MI, or nonfatal stroke), linagliptin demonstrated noninferiority to placebo (12.4% vs 12.1%, respectively; HR, 1.02; 95% CI, 0.89 to 1.17; p < 0.001 for noninferiority; p = 0.74 for superiority). The risk of a secondary outcome event (composite of death due to renal failure, end-stage renal disease [ESRD], or ≥ 40% decrease in estimated glomerular filtration rate [eGFR] from baseline) did not differ significantly in the linagliptin and placebo groups (9.4% vs 8.8%, respectively; HR, 1.04; 95% CI, 0.89 to 1.22; p = 0.62) *(Rosenstock et al 2019)*.

Saxagliptin-containing products

- In the following 10 pivotal trials described in the Onglyza prescribing information (2017) and published as cited, saxagliptin has been shown to have activity for improving glucose control when:
  - used as monotherapy vs placebo *(Frederich et al 2012, Rosenstock et al 2009[b])*
  - used as add-on combination therapy with metformin vs placebo + metformin *(DeFronzo et al 2009)*
  - co-administered with metformin in treatment-naïve patients vs placebo + metformin *(Jadzinsky et al 2009)*
  - used as add-on combination therapy with a TZD vs placebo + a TZD *(Hollander et al 2009)*
  - used as add-on combination therapy with glyburide (an SFU) vs placebo + glyburide *(Chacra et al 2009)*
  - used as add-on combination therapy with metformin vs glipizide add-on combination therapy with metformin *(Goke et al 2013)*
  - used as add-on combination therapy with insulin (+/- metformin) vs placebo + insulin (+/- metformin) *(Barnett et al 2012[a])*
  - used as add-on combination therapy with metformin + an SFU vs placebo + metformin + an SFU *(Moses et al 2014)*
  - used as monotherapy vs placebo in patients with renal impairment *(Nowicki et al 2011)*
- There have been no clinical efficacy or safety studies conducted with Kombiglyze XR to characterize its effect on HbA1c reduction; however, the bioequivalence of Kombiglyze XR to saxagliptin and extended-release metformin tablets co-administered as individual tablets has been demonstrated.
- The bioequivalence of saxagliptin/dapagliflozin fixed-dose combination tablets to the co-administration of the individual tablets in healthy subjects has been demonstrated *(Vakkalagadda et al 2016)*. Efficacy and safety were observed as add-on therapy with saxagliptin in patients on dapagliflozin plus metformin at 24 weeks *(Matthaei et al 2015)* and at 52 weeks *(Matthaei et al 2016)*; with dapagliflozin added to saxagliptin plus metformin at 24 weeks *(Mathieu et al 2015[a])* and 52 weeks *(Mathieu et al 2016)*; and with saxagliptin plus dapagliflozin addition vs the single addition of saxagliptin or dapagliflozin to metformin at 24 weeks *(Rosenstock et al 2015[b])*.
- **CV outcomes** *(Scirica et al 2013, Scirica et al 2014)*
  - The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR-TIMI 53) was a Phase 4, DB, PC, MC, RCT (N = 16,492) evaluating the safety and efficacy of saxagliptin vs placebo with respect to CV outcomes in patients with T2DM who were at risk for CV events. The primary endpoint was a composite of CV death, MI, or ischemic stroke.
    - A primary endpoint event occurred in 613 patients in the saxagliptin group and in 609 patients in the placebo group (7.3% and 7.2%, respectively, according to 2-year Kaplan–Meier estimates; HR with saxagliptin = 1.00; 95% CI: 0.89 to 1.12; p = 0.99 for superiority; p < 0.001 for noninferiority [pre-specified noninferiority margin of 1.3 for the HR]).

- The major secondary endpoint of a composite of CV death, MI, stroke, hospitalization for unstable angina, coronary revascularization, or HF occurred in 1059 patients in the saxagliptin group and in 1034 patients in the placebo group (12.8% and 12.4%, respectively, according to 2-year Kaplan–Meier estimates; HR = 1.02; 95% CI: 0.94 to 1.11; p = 0.66).
- More patients in the saxagliptin group than in the placebo group were hospitalized for HF (3.5% vs 2.8%, HR = 1.27; 95% CI, 1.07 to 1.51; p = 0.007).
- More patients in the saxagliptin group than the placebo group experienced death from any cause, although the difference was not statistically significant (n = 420/8280 [5.1%] vs 378/8212 [4.6%], HR = 1.11; 95% CI, 0.96 to 1.27; p = 0.15).

Sitagliptin-containing products

- In the following 11 pivotal trials described in the Januvia prescribing information (2017) and published as cited, sitagliptin has been shown to have activity for improving glucose control when:
  - used as monotherapy vs placebo *(Aschner et al 2006, Raz et al 2006)*
  - used as monotherapy vs placebo in patients with chronic renal insufficiency *(Chan et al 2008)*
  - used as add-on combination therapy with metformin vs placebo + metformin *(Charbonnel et al 2006)*
  - used as initial combination therapy with metformin vs placebo or sitagliptin or metformin monotherapy *(Goldstein et al 2007)*
  - used in combination with metformin vs glipizide + metformin *(Nauck et al 2007)*
  - used as add-on combination therapy with pioglitazone vs placebo + pioglitazone *(Rosenstock et al 2006)*
  - used as initial combination therapy with pioglitazone vs pioglitazone monotherapy *(Yoon et al 2011)*
  - used as add-on combination therapy with metformin and rosiglitazone vs placebo + metformin + rosiglitazone *(Scott et al 2008)*
  - used as add-on combination therapy with glimepiride +/- metformin vs placebo + glimepiride +/- metformin *(Hermansen et al 2007)*
  - used as add-on combination therapy with insulin +/- metformin vs placebo + insulin +/- metformin *(Mathieu et al 2015[b])*
- While the co-administration of sitagliptin and metformin has been studied in patients with T2DM inadequately controlled on diet and exercise and in combination with other antihyperglycemic agents, there have been no clinical efficacy studies conducted with Janumet, the sitagliptin/metformin combination product; bioequivalence of Janumet with co-administered sitagliptin and metformin hydrochloride tablets was demonstrated (*Drugs@FDA 2018*).
- There have been no clinical efficacy or safety studies conducted with Janumet XR to characterize its effect on HbA1c reduction, however, bioequivalence of Janumet XR tablets with co-administered sitagliptin and extended-release metformin tablets has been demonstrated for all tablet strengths (*Drugs@FDA 2018*).
- Steglujan, the combination product of sitagliptin and ertugliflozin, showed significant improvements in HbA1c over 26 weeks compared with individual agents in patients uncontrolled on metformin alone, compared with placebo in patients uncontrolled on diet and exercise alone, and when ertugliflozin was added vs placebo in patients uncontrolled on metformin and sitagliptin *(Dagogo-Jack et al 2018, Miller et al 2018, Pratley et al 2017).*
- **CV outcomes** *(Green et al 2015)*
  - The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) was a Phase 3, DB, PC, MC, RCT (N = 14,671 ITT population) evaluating CV outcomes after treatment with sitagliptin in patients with T2DM, inadequate glycemic control, and established CV disease. The primary CV outcome was a composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina.
    - Overall, the primary outcome occurred in 839 patients in the sitagliptin group (11.4%; 4.06 per 100 person-years) and 851 patients in the placebo group (11.6%; 4.17 per 100 person-years). Sitagliptin was noninferior to placebo for the primary composite CV outcome (HR = 0.98; 95% CI, 0.88 to 1.09; p < 0.001). Rates of hospitalization for HF did not differ between the 2 groups (HR = 1.00; 95% CI, 0.83 to 1.20; p = 0.98).

Comparative studies

- Many clinical trials are available comparing DPP-4 inhibitors to placebo and to alternative antihyperglycemic agents, both as monotherapy and in combination regimens. Consistent with treatment guidelines, most trials have evaluated DPP-4 inhibitors not as initial therapy, but as add-on therapy to provide additional glucose control to patients who are not at their goal HbA1c on 1 or more existing therapies. Most trials evaluated HbA1c as a primary outcome measure,

with or without also measuring fasting plasma glucose (FPG), postprandial glucose (PPG), and other metabolic outcomes. Some studies have evaluated longer-term diabetes outcomes, such as CV outcomes or overall mortality.

- Although comparative trials between different DPP-4 inhibitors are uncommon, 1 trial comparing saxagliptin 5 mg daily to sitagliptin 100 mg daily demonstrated that saxagliptin was noninferior to sitagliptin for HbA1c reduction (-0.52% in the saxagliptin group vs -0.62% in the sitagliptin group, adjusted mean decrease in HbA1c = 0.09%; 95% CI, -0.01 to 0.2; p-value not reported). Sitagliptin decreased FPG to a greater extent than saxagliptin (-16.2 vs -10.8 mg/dL, respectively; mean difference = 5.42 mg/dL; 95% CI: 1.37 to 9.47 mg/dL; p-value not reported) *(Scheen et al 2010)*.
- A meta-analysis (MA) of 80 RCTs of incretin-based therapies (DPP-4 inhibitors and GLP-1 agonists) in patients with T2DM (N = 41,807) demonstrated that the highest maintenance doses of the DPP-4 inhibitors resulted in mean HbA1c changes from baseline of -0.6 to -1.1%. Each DPP-4 inhibitor demonstrated similar mean reductions from baseline in HbA1c when adjusted for baseline differences: alogliptin -0.70% (95% CI: -0.90 to -0.50%), linagliptin -0.60% (95% CI: -0.80 to -0.40%), saxagliptin -0.71% (95% CI: -0.89 to -0.54%), and sitagliptin -0.70% (95% CI: -0.78 to -0.63%) *(Aroda et al 2012).*
- A systematic review (SR) and MA of 27 reports of 19 studies in patients with T2DM (N = 13,881) demonstrated that in comparison with metformin, DPP-4 inhibitors were associated with a smaller decline in HbA1c [weighted mean difference = 0.2; 95% CI, 0.08 to 0.32; I^2 = 60%] and a lower chance of attainment of the HbA1c goal of < 7% (risk ratio in favor of metformin = 1.18; 95% CI, 1.07 to 1.29; I^2 = 34%). As second-line treatment, DPP-4 inhibitors less effectively reduced HbA1c vs SFUs (weighted mean difference = 0.07; 95% CI, 0.02 to 0.13) and GLP-1 agonists (weighted mean difference = 0.49; 95% CI, 0.31 to 0.67), but were equally effective as pioglitazone (weighted mean difference = 0.09; 95% CI, -0.07 to 0.24) *(Karagiannis et al 2012)*.
- An SR and MA of randomized and observational studies that examined HF and hospitalization for HF identified 43 RCTs (N = 68,775 patients) and 12 observational studies (9 cohort studies + 3 nested case-control studies in N = 1,777,358 total patients); the length of follow-up ranged from 12 to 206 weeks. Thirty-eight (38) trials reported 75 HF events occurring in 28,292 patients who were treated with at least 1 drug (raw event rate 0.27% vs 0.26% for controls [odds ratio (OR) = 0.97, 95% CI: 0.61 to 1.56, I^2 = 0%]). Overall, 1174 events of admission for HF occurred in 37,028 patients (raw event rate 3.4% for DPP-4 inhibitors vs 3.0% for controls). Pooling across trials showed a borderline increase in the risk of hospital admission for HF in patients with T2DM using DPP-4 inhibitors vs control (OR = 1.13, 95% CI: 1.00 to 1.26; I^2 = 0%) *(Li et al 2016)*.
- An SR and MA by Verma et al (2017) attempted to examine the totality of RCT evidence concerning the association between DPP-4 inhibitors and HF. A total of 100 RCTs (N = 79,867) were identified, including the 3 large, CV outcomes studies, EXAMINE, SAVOR-TIMI 53, and TECOS. A total of 96% (1192/1244) of HF events were pre-specified, blindly adjudicated, and required hospital admission. Pooled results suggested a 13% increase in HF (relative risk [RR] = 1.13; 95% CI, 1.01 to 1.26, I^2 = 0%; 32 RCTs, N = 54,640 and 1244 events). When including only the 3 large RCTs, the increase was similar, but not significant (RR = 1.14; 95% CI, 0.97 to 1.32; 3 RCTs, N = 36,543 and 1169 adjudicated events; number needed to harm = 246) owing to heterogeneity (I^2 = 42%), which lead to wider CIs, because SAVOR-TIMI 53 showed increased HF, while TECOS showed no effect.
- A network MA indirectly evaluated comparative risks for HF among DPP-4 inhibitors *(Guo 2017)*. Analysis of 50 RCTs demonstrated that compared with placebo, no increased risk of HF events was seen for sitagliptin (RR = 0.86; 95% CI, 0.43 to 1.57) or saxagliptin (RR = 0.84; 95% CI, 0.33 to 1.61), but alogliptin was associated with a higher risk of events (RR = 2.13; 95% CI, 1.06 to 6.26). Among agents available in the United States, indirect comparisons favored sitagliptin over alogliptin (RR = 0.40; 95% CI, 0.11 to 0.96), sitagliptin over linagliptin (RR = 0.31; 95% CI, 0.09 to 0.95), and saxagliptin over linagliptin (RR = 0.30; 95% CI, 0.07 to 0.97). The product with the highest probability to be the safest with regard to HF risk was saxagliptin (26.56%), followed by sitagliptin (20.76%), linagliptin (0.25%), and alogliptin (0.12%).
- An SR of literature concerning the overall CV and long-term safety of DPP-4 inhibitors in patients with T2DM identified 36 DB, PC, RCTs (N = 54,664). Overall, there were no significant differences in all-cause mortality (RR = 1.03; 95% CI, 0.95 to 1.12), CV mortality (RR = 1.02; 95% CI, 0.92 to 1.12), MI (RR = 0.98; 95% CI, 0.89 to 1.08), stroke (RR = 1.02; 95% CI, 0.88 to 1.17), renal failure (RR = 1.06; 95% CI, 0.88 to 1.27), severe hypoglycemia (RR = 1.14; 95% CI, 0.95 to 1.36), and pancreatic cancer (RR = 0.54; 95% CI, 0.28 to 1.04) with the use of DPP-4 inhibitors. However, the DDP-4 inhibitors were associated with an increased risk of HF (RR = 1.13; 95% CI, 1.01 to 1.26) and acute pancreatitis (RR = 1.57; 95% CI, 1.03 to 2.39) *(Rehman et al 2017)*. A subsequent MA evaluating acute pancreatitis across 5 RCTs found significant increases in risk (RR = 1.67; 95% CI, 1.08 to 2.59), but similar results were not observed in a pooled analysis of 3 cohort studies (HR = 1.06; 95% CI, 0.89 to 1.26) *(Chen et al 2017).*

- An SR to evaluate the association between DPP-4 inhibitors/GLP-1 receptor agonists and MACE in patients with T2DM identified 36 articles that included a total of 11 pooled analyses, 17 MAs, and 8 RCTs (including secondary analyses). Over the short-term (up to 4 years), those exposed to a DPP-4 inhibitor or a GLP-1 receptor agonist were not at increased risk for MACE or its component endpoints vs comparators. Two MAs showed a significant reduction in the incidence of MACE associated with overall DPP-4 inhibitor therapy, but the beneficial effect was not observed in other MAs that included larger CV outcomes studies (ie, EXAMINE, SAVOR-TIMI 53, TECOS). An increased rate of HF hospitalizations was associated with saxagliptin *(Manucci et al 2017)*.
- A network MA evaluated the CV effects of empagliflozin compared to DPP-4 inhibitors in patients with T2DM with established CV disease or at high risk for CV outcomes. The analysis pooled 4 studies and found that empagliflozin was superior to saxagliptin (HR, 0.60; 95% credible interval [CrI], 0.46 to 0.80) and sitagliptin (HR, 0.60; 95% CrI, 0.46 to 0.79) in reducing the risk of CV mortality. Similar results were found for all-cause mortality (empagliflozin vs saxagliptin: HR, 0.61; 95% CrI, 0.49 to 0.76; and vs sitagliptin: HR, 0.67; 95% CrI, 0.54 to 0.83) *(Balijepalli et al 2018)*.
- In a network MA of 236 trials (N = 176,310) comparing DPP-4 inhibitors, SGLT2 inhibitors, and GLP-1 agonists, DPP-4 inhibitors were not associated with significantly lower all-cause mortality compared to placebo or no treatment (absolute risk difference [RD], 0.1%; HR, 1.02; 95% CrI, 0.94 to 1.11). SGLT2 inhibitors (absolute RD, -0.9%; HR, 0.78; 95% CrI, 0.68 to 0.90) and GLP-1 agonists (absolute RD, -0.5%; HR, 0.86; 95% CrI, 0.77 to 0.96) were associated with significantly lower mortality compared to DPP-4 inhibitors *(Zheng et al 2018)*.

CLINICAL GUIDELINES

Overview

- Professional society guidelines are consistent in recommending metformin as the optimal first-line pharmacologic therapy for treatment-naïve patients with T2DM, unless the patient has contraindications or intolerance. DPP-4 inhibitors are among the second-line options for subsequent therapy. All guidelines emphasize individualized therapy based upon patient-specific factors such as comorbidities, weight, risk of hypoglycemia, and duration of diabetes *(ADA 2019, Copeland et al 2013, Davies et al 2018, Garber et al 2019)*.
- A 2018 American College of Cardiology expert consensus decision pathway on CV risk reduction in patients with T2DM and atherosclerotic CV disease (ASCVD) suggests adding an SGLT2 inhibitor or GLP-1 receptor agonist that has demonstrated beneficial CV outcomes to other guideline-directed therapy for diabetes (specifically, metformin). Among the SGLT2 inhibitors with CV outcome data at the time that the pathway was written (canagliflozin and empagliflozin), empagliflozin was the preferred SGLT2 inhibitor based on the available evidence and overall risk to benefit ratio *(Das et al 2018)*.

- **ADA/European Association for the Study of Diabetes (EASD): Management of Hyperglycemia in Type 2 Diabetes, 2018** *(Davies et al 2018)*
  - The goals of T2DM therapy are to prevent or delay complications and maintain quality of life, which requires glycemic control, CV risk factor management, regular follow-up, and a patient-centered approach to enhance patient engagement in self-care activities. Careful consideration of patient-specific factors and preferences must inform the process of individualizing treatment goals and strategies.
  - Due to new evidence of benefit with specific agents in the reduction of mortality, HF, and progression of renal disease, the overall approach to glucose-lowering medication in T2DM for the ADA/EASD consensus report was updated in 2018. A history of CVD, chronic kidney disease (CKD), and HF should be taken into consideration early in the process of treatment selection. Additionally, the guideline recommends early consideration of weight, hypoglycemic risk, treatment cost, and other patient-related factors that may influence the choice of drug therapy.
    - Among patients with T2DM who have established ASCVD, SGLT2 inhibitors or GLP-1 receptor agonists with proven CV benefit are recommended as part of glycemic management.
    - For patients with ASCVD with concomitant HF, SGLT2 inhibitors are recommended.
    - For patients with T2DM and CKD (with or without ASCVD), an SGLT2 inhibitor shown to reduce CKD progression should be considered. If SGLT2 inhibitors are contraindicated or not preferred, a GLP-1 receptor agonist shown to reduce CKD progression should be considered.
  - Initial monotherapy: Metformin remains the preferred drug for initial monotherapy based on its efficacy, safety, tolerability, low cost, and extensive clinical experience.

- Add-on to metformin: The selection of a second agent added to metformin is based on patient preference and clinical characteristics. Important clinical characteristics include the presence of established ASCVD and other comorbidities such as HF or CKD; the risk for specific AEs, particularly hypoglycemia and weight gain; as well as safety, tolerability, and cost.
- Intensification beyond 2 medications: Intensification of treatment beyond dual therapy to maintain glycemic targets requires consideration of the impact of medication side effects on comorbidities, as well as the burden of treatment and cost.
- Addition of injectable medications: For patients who require the greater glucose-lowering effect of an injectable medication, GLP-1 receptor agonists are preferred over insulin. For patients with extreme and symptomatic hyperglycemia, insulin is recommended.
- Beyond basal insulin: Patients who are unable to maintain glycemic targets on basal insulin in combination with oral medications can have treatment intensified with GLP-1 receptor agonists, SGLT2 inhibitors, or prandial insulin.

- **ADA: Standards of Medical Care in Diabetes – 2019** *(ADA 2019)*
  - Pharmacological therapy for T2DM:
    - Metformin (if not contraindicated and if tolerated) is the preferred initial pharmacological agent for T2DM (level A).
    - Metformin should be continued when used in combination with other agents, including insulin, if not contraindicated and if tolerated (level A).
    - Dual therapy should be considered in patients with newly diagnosed T2DM who have HbA1c ≥ 1.5% above their glycemic target (level E).
    - Early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when HbA1c levels (> 10%) or blood glucose levels (> 300 mg/dL) are very high (level E).
    - A patient-centered approach should be used to guide the choice of pharmacologic therapy. Considerations include comorbidities (ASCVD, HF, CKD), hypoglycemia risk, impact on weight, cost, risk for side effects, and patient preferences (level E).
    - In patients with T2DM and established ASCVD, SGLT2 inhibitors or GLP-1 receptor agonists with demonstrated CVD benefit are recommended as part of the antihyperglycemic regimen (level A).
    - In patients with T2DM and established ASCVD with a high risk of or existing HF, SGLT2 inhibitors are preferred (level C).
    - In patients with T2DM and CKD, use of SGLT2 inhibitors or GLP-1 receptor agonists shown to reduce the risk of CKD progression, CV events, or both should be considered (level C).
    - In most patients who require the greater glucose-lowering effect of an injectable medication, GLP-1 receptor agonists are preferred over insulin (level B).
    - The medication regimen should be reevaluated at regular intervals (every 3 to 6 months) and adjusted as needed to incorporate new patient factors (level E).
  - Initial therapy
    - Metformin should be initiated at the time T2DM is diagnosed if there are no contraindications.
    - For patients with contraindications or intolerance to metformin, initial therapy with an SGLT2 inhibitor, GLP-1 receptor agonist, DPP-4 inhibitor, TZD, SFU (2nd generation), or insulin should be considered based on patient factors.
  - Combination therapy
    - Dual therapy is recommended for patients who do not achieve their HbA1c goal after 3 months of monotherapy.
    - For patients without ASCVD or CKD, an agent from any of the 6 preferred classes (SFU, TZD, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or basal insulin) can be added to metformin, with the choice of agent based on drug-specific effects (ie, avoidance of adverse effects such as hypoglycemia and weight gain) and patient factors (ie, cost and personal preference).
    - For patients with ASCVD, HF, or CKD, the best choice for add-on therapy is a GLP-1 receptor agonist or SGLT2 inhibitor with demonstrated benefit.
    - Similar considerations are applied in patients who require a third agent to achieve glycemic goals.

Table 6. ADA Factors to Consider for Antihyperglycemic Therapies in T2DM

Class*	Efficacy	Hypoglycemia	Weight	ASCVD	CHF	Route	DKD	Additional

								considerations
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Oral	Neutral	GI AEs common B12 deficiency
SGLT2i	Intermediate	No	Loss	Benefit: canagliflozin, empagliflozin	Benefit: canagliflozin, empagliflozin	Oral	Benefit: canagliflozin, empagliflozin	Boxed warning for amputation: canagliflozin Genitourinary infections
GLP-1ra	High	No	Loss	Neutral: lixisenatide Benefit: liraglutide > semaglutide > exenatide ER	Neutral	SQ	Benefit: liraglutide	Boxed warning for thyroid C-cell tumors (liraglutide, albiglutide, dulaglutide, exenatide ER)
DPP-4i	Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin, alogliptin	Oral	Neutral	Potential risk of acute pancreatitis Joint pain
TZD	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Oral	Neutral	Boxed warning for CHF (pioglitazone, rosiglitazone)
SFU (2nd generation)	High	Yes	Gain	Neutral	Neutral	Oral	Neutral	FDA special warning on increased risk of CV mortality based on studies of an older SFU (tolbutamide)
Insulin	Highest	Yes	Gain	Neutral	Neutral	SQ	Neutral	Injection site reactions

Abbreviations: AE = adverse event; ASCVD = atherosclerotic cardiovascular disease; CHF = congestive heart failure; CV = cardiovascular; DKD = diabetic kidney disease; DPP-4i = dipeptidyl peptidase 4 inhibitor; ER = extended-release; GI = gastrointestinal; GLP-1ra = glucagon-like peptide-1 receptor agonist; SFU = sulfonylurea; SGLT2i = sodium-glucose cotransporter-2 inhibitor; SQ = subcutaneous; T2DM = type 2 diabetes mellitus; TZD = thiazolidinediones

* Other antidiabetic drugs not shown in above table (eg, inhaled insulin, alpha-glucosidase inhibitors (AGIs), colesevelam, bromocriptine, and pramlintide) may be tried in specific situations; however, considerations include modest efficacy in T2DM, frequency of administration, potential for drug interactions, cost, and/or side effects.

- **American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) - Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm** *(Garber et al 2019)*
  - Founding principles of the Comprehensive Type 2 Diabetes Management Algorithm:
    - Lifestyle optimization is essential for all patients with diabetes.
    - Minimizing the risk of both severe and non-severe hypoglycemia is a priority. Minimizing risk of weight gain is also a priority.
    - The HbA1c target should be individualized based on numerous factors, such as age, life expectancy, comorbid conditions, duration of diabetes, risk of hypoglycemia or adverse consequences from hypoglycemia, patient motivation, and adherence. A target HbA1c ≤ 6.5% is considered optimal if it can be achieved in a safe and affordable manner, but higher targets may be appropriate for certain individuals and may change for a given individual over time.
    - Glycemic control targets include fasting and post-prandial glucose as determined by self-monitoring of blood glucose.
    - The choice of diabetes therapies must be individualized based on attributes specific to both patients and the medications themselves. Medication attributes include antihyperglycemic efficacy, mechanism of action, risk of inducing hypoglycemia, risk of weight gain, other AEs, tolerability, ease of use, likely adherence, cost, and safety or risk reduction in heart, kidney, or liver disease. Patient-specific considerations include initial A1C, duration of T2D, and obesity status.
      - The choice of therapy depends on the individual patient's cardiac, cerebrovascular, and renal status. Combination therapy is usually required and should involve agents with complementary mechanisms of action.
    - Therapy must be evaluated frequently (eg, every 3 months) until the patient is stable, using multiple criteria (eg, HbA1c, self-monitoring of blood glucose records, lipid and blood pressure levels, hypoglycemia events, AEs).
  - Glycemic control algorithm for T2DM:

- In patients with recent-onset T2DM or mild hyperglycemia (HbA1c < 7.5%), lifestyle therapy plus antihyperglycemic monotherapy (preferably with metformin) is recommended. For patients with ASCVD or CKD, GLP-1 receptor agonists and SGLT2 inhibitors with proven benefits may be preferred.
  - Other acceptable alternatives to metformin include DPP-4 inhibitors and TZDs; AGIs, SFUs, and meglitinides may also be appropriate as monotherapy for select patients.
- In patients who do not achieve their HbA1c goal after 3 months of monotherapy or patients who present with HbA1c ≥ 7.5%, dual therapy should be started by adding 1 of the following agents to metformin (in order of preference): GLP-1 receptor agonist, SGLT2 inhibitor, DPP-4 inhibitor, TZD, basal insulin, colesevelam, bromocriptine quick release (QR), AGI, SFU, or meglitinide.
- If dual therapy does not achieve the HbA1c goal in 3 months, triple therapy should be started by adding 1 of the following agents to metformin plus a second-line agent (in order of preference): GLP-1 receptor agonist, SGLT2 inhibitor, TZD, basal insulin, DPP-4 inhibitor, colesevelam, bromocriptine QR, AGI, SFU, or meglitinide.
- If triple therapy fails to achieve the HbA1c goal in 3 months, then the patient should proceed to or intensify insulin therapy.
- In patients with entry HbA1c > 9.0%, dual therapy or triple therapy is recommended if the patient is asymptomatic. If the patient is symptomatic, insulin therapy alone or in combination with other agents is recommended.

○ DPP-4 inhibitor-specific information:

- DPP-4 inhibitors have modest A1C-lowering properties, are weight-neutral, have low risk of hypoglycemia, and neutral with respect to CV outcomes.
- DPP-4 inhibitors should be used with caution in patients with a history of pancreatitis (and stopped if pancreatitis occurs), although a causative association has not been established.
- A possible slight increased risk of HF with saxagliptin and alogliptin was found in the respective CV outcome trials.

Table 7. AACE/ACE Profiles of Antidiabetic Medications

	Hypoglycemia	Weight	Renal/GU	GI	Cardiac	Bone	Ketoacidosis
Metformin	Neutral	Slight loss	eGFR < 30: contraindicated	Moderate	Neutral	Neutral	Neutral
GLP-1ra	Neutral	Loss	Possible benefit: liraglutide Exenatide not indicated CrCl < 30	Moderate	Liraglutide FDA approved for prevention of MACE	Neutral	Neutral
SGLT2i	Neutral	Loss	Genital mycotic infections Not indicated eGFR < 45 Possible CKD benefit	Neutral	Empagliflozin FDA approved to reduce CV mortality Canagliflozin FDA approved to reduce MACE	Neutral	DKA can occur
DPP-4i	Neutral	Neutral	Dose adjustment necessary (except linagliptin) Albuminuria reduction	Neutral	Alogliptin, saxagliptin: Possible increased HHF	Neutral	Neutral
AGI	Neutral	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral
TZD	Neutral	Gain	Neutral	Neutral	Moderate CHF risk May reduce stroke risk	Moderate fracture risk	Neutral
SFU	Moderate/severe	Gain	More hypoglycemia risk	Neutral	Possible ASCVD risk	Neutral	Neutral
Meglitinide	Mild	Gain	More hypoglycemia risk	Neutral	Possible ASCVD risk	Neutral	Neutral
Colesevelam	Neutral	Neutral	Neutral	Mild	ASCVD benefit	Neutral	Neutral
Bromocriptine QR	Neutral	Neutral	Neutral	Moderate	Safe	Neutral	Neutral
Insulin	Moderate to severe	Gain	More hypoglycemia risk	Neutral	CHF risk	Neutral	Neutral
Pramlintide	Neutral	Loss	Neutral	Moderate	Neutral	Neutral	Neutral

Abbreviations: AGI = alpha-glucosidase inhibitor; ASCVD = atherosclerotic cardiovascular disease; CHF = congestive heart failure; CrCl = creatinine clearance; CV = cardiovascular; DKA = diabetic ketoacidosis; DPP-4i = dipeptidyl peptidase 4 inhibitor; eGFR = estimated glomerular filtration rate; FDA = Food and Drug Administration; GI = gastrointestinal; GLP-1ra = glucagon-like peptide-1 receptor agonist; GU = genitourinary; HHF = hospitalization for heart

failure; MACE = major adverse cardiovascular events; QR = quick release; SFU = sulfonylurea; SGLT2i = sodium-glucose cotransporter-2 inhibitor; TZD = thiazolidinedione

SAFETY SUMMARY

- All of the metformin combination products contain a boxed warning for lactic acidosis and are contraindicated in patients with renal impairment and in patients with acute or chronic metabolic acidosis, including diabetic ketoacidosis. Alogliptin/pioglitazone contains a boxed warning for CHF and is contraindicated for initiation in patients with established New York Heart Association (NYHA) Class III or IV HF. Linagliptin/empagliflozin and sitagliptin/ertugliflozin are contraindicated in patients with severe renal impairment, ESRD, or in those receiving dialysis. Saxagliptin/dapagliflozin is contraindicated in patients with moderate to severe renal impairment (eGFR < 45 mL/min/1.73 m^2), ESRD, or patients on dialysis.
- Warnings and precautions common to all of the DPP-4 and DPP-4-combination products concern the risks of acute pancreatitis, HF, hypersensitivity reactions, arthralgia, postmarketing reports of bullous pemphigoid requiring hospitalization, and the increased risk of hypoglycemia when added to an insulin secretagogue or insulin therapy.
  - Warnings/precautions common to all of the metformin-containing products concern hepatic impairment, potentiation of metformin effects by alcohol, vitamin B12 deficiency, radiologic studies/surgical procedures necessitating temporary medication discontinuation, hypoxic states, changes in clinical status, loss of blood glucose control, and interactions with concomitant medications. There is the potential for unintended pregnancy with premenopausal women as therapy with metformin may result in ovulation in some premenopausal anovulatory women. Drug interactions include:
    - Concomitant use of topiramate and other carbonic anhydrase inhibitors with metformin may increase the risk of lactic acidosis; frequent monitoring of patients should be considered.
    - Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (eg, ranolazine, vandetanib, dolutegravir, cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis; benefits and risks of concomitant use should be weighed.
    - Alcohol is known to potentiate the effect of metformin on lactate metabolism; patients should be warned against excessive alcohol intake while on metformin-containing products.
    - Co-administration with an insulin secretagogue (eg, SFU) or insulin may require lower doses of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.
    - Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control; they include thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving metformin-containing products, the patient should be closely observed to maintain adequate glycemic control.
  - Warnings/precautions specific to the SGLT2 inhibitors (ie, dapagliflozin contained in Qtern, empagliflozin contained in Glyxambi, and ertugliflozin contained in Steglujan) concern the risks of genital mycotic infections, hypotension, increased low density lipoprotein cholesterol, ketoacidosis, urosepsis and pyelonephritis, necrotizing fasciitis of the perineum, and the need for renal function monitoring. Drug interactions include:
    - Co-administration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion.
    - Co-administration of empagliflozin with insulin or insulin secretagogues increases the risk for hypoglycemia.
    - Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Alternative methods for monitoring glycemic control should be used.
    - Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors; alternative methods for monitoring glycemic control should be used.
  - Warnings/precautions specific to pioglitazone (contained in Oseni) concern the risks of edema, fractures, urinary bladder tumors, macular edema, and changes in ovulation. Drug interactions include:
    - The maximum recommended dose of pioglitazone is 15 mg daily if used in combination with gemfibrozil or other strong CYP2C8 inhibitors due to increased exposure and half-life of pioglitazone.
    - Inducers of CYP2C8 may significantly decrease the exposure of pioglitazone. If an inducer of CYP2C8 is started or stopped during treatment with Oseni, changes in antidiabetic therapy may be needed on the basis of clinical response, but should not exceed the maximum recommended daily dose of 45 mg for pioglitazone.

- Post-marketing reports of hepatic failure, both fatal and non-fatal, have been seen with alogliptin; the warning also appears in the labeling of alogliptin/metformin and alogliptin/pioglitazone.
- Worsening renal function, including acute renal failure sometimes requiring dialysis, has been reported in patients treated with sitagliptin with or without metformin.

- The DPP-4 inhibitors were well tolerated in short-term studies; there are no effects on body weight or risk of hypoglycemia (in the absence of concomitant treatment with insulin or SFUs). Furthermore, an SR and MA demonstrated that DPP-4 inhibitors are well tolerated with an incidence of AEs similar to placebo *(Gooßen et al 2012)*.
  - Commonly reported AEs include headache, nasopharyngitis, and upper respiratory tract infection.
  - Despite the growing body of evidence gleaned from CV outcomes trials, the long-term safety with DPP-4 inhibitors has not been established *(Dungan 2017)* and there have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with DPP-4 inhibitors.

DPP-4 inhibitors and HF

- Following an in-depth review of results from the SAVOR-TIMI 53 and EXAMINE CV outcomes studies by the FDA, a warning concerning the increased risk of HF was added to all products containing alogliptin (ie, Nesina, Kazano, Oseni) and saxagliptin (ie, Onglyza, Kombiglyze XR, Qtern) in April 2016.
  - The risks and benefits of these products should be considered prior to their initiation in patients at risk for HF, such as those with a prior history of HF and a history of renal impairment. Patients should be observed for signs and symptoms of HF during therapy.
  - Patients should be advised of the characteristic symptoms of HF and should be instructed to immediately report such symptoms.
  - If HF develops, patients should be evaluated and managed according to the current standards of care; discontinuation of these products should also be considered.
- On August 10, 2017, the labeling of all linagliptin- (ie, Glyxambi, Tradjenta, Jentadueto, Jentadueto XR) and sitagliptin-containing (ie, Januvia, Janumet, Janumet XR) products was updated with a similar HF warning that the FDA believed was warranted based on the association between DPP-4 inhibitor treatment and HF that was observed in CV outcomes trials [ie, SAVOR-TIMI 53 and EXAMINE] for the other 2 members of the DPP-4 inhibitor class [ie, saxagliptin and alogliptin]. The risks and benefits of these products should be considered in patients with known risk factors for HF; patients should be monitored for signs and symptoms of HF while on treatment.

DOSING AND ADMINISTRATION

Table 8. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Alogliptin-containing products				
Nesina (alogliptin)	Tablets	Oral	Daily	Taken with or without food Must be dose-adjusted in cases of moderate and severe renal impairment
Kazano (alogliptin/ metformin HCl)	Tablets	Oral	Two times daily	Individualize starting dose based on patient's current regimen; taken with food with gradual dose escalation to minimize GI AEs due to metformin; tablets must not be split before swallowing Not recommended in patients with an eGFR between 30 and 60 mL/min/1.73 m^2; contraindicated in patients with

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				an eGFR < 30 mL/min/1.73 m^2 Not recommended in patients with hepatic impairment
Oseni (alogliptin/ pioglitazone)	Tablets	Oral	Daily	Individualize dosing based on current regimen and medical condition; taken with or without food; tablets must not be split before swallowing Must be dose-adjusted in cases of moderate renal impairment; not recommended in severe renal impairment
Linagliptin-containing products				
Tradjenta (linagliptin)	Tablets	Oral	Daily	Taken with or without food
Glyxambi (linagliptin/ empagliflozin)	Tablets	Oral	Daily	Taken with or without food Should not be initiated in patients with an eGFR < 45 mL/min/1.73 m^2; should be discontinued in patients whose eGFR falls below 45 mL/min/1.73 m^2
Jentadueto (linagliptin/ metformin HCl)	Tablets	Oral	Two times daily	Individualize starting dose based on the patient's current regimen; taken with food with gradual dose escalation to minimize GI AEs due to metformin Not recommended in patients with an eGFR between 30 and 45 mL/min/1.73 m^2; contraindicated in patients with an eGFR < 30 mL/min/1.73 m^2 Not recommended in patients with hepatic impairment
Jentadueto XR (linagliptin/ metformin HCl extended release)	Tablets	Oral	Daily	Individualized based on patient's current regimen, effectiveness, and tolerability; taken with food; tablets must be swallowed whole and never split, crushed, dissolved, or chewed Not recommended in patients with an eGFR between 30 and 45 mL/min/1.73 m^2; contraindicated in patients with an eGFR < 30 mL/min/1.73 m^2

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Not recommended in patients with hepatic impairment
Saxagliptin-containing products				
Onglyza (saxagliptin)	Tablets	Oral	Daily	Taken with or without food; tablets must not be split or cut Must be dose-adjusted in cases of eGFR < 45mL/min/1.73 m^2
Kombiglyze XR (saxagliptin/ metformin HCl extended release)	Tablets	Oral	Daily	Individualized based on patient's current regimen, effectiveness, and tolerability; taken with an evening meal with gradual dose titration to reduce the GI side effects associated with metformin; tablets must be swallowed whole and never crushed, cut, or chewed Not recommended in patients with an eGFR between 30 and 45 mL/min/1.73 m^2; contraindicated in patients with an eGFR < 30 mL/min/1.73 m^2 Not recommended in patients with hepatic impairment
Qtern (saxagliptin/ dapagliflozin)	Tablets	Oral	Daily	Taken with or without food; tablets must not be split or cut Should not be initiated in patients with an eGFR < 60 mL/min/1.73 m^2; should be discontinued in patients whose eGFR falls below 60 mL/min/1.73 m^2; contraindicated in patients with an eGFR < 45 mL/min/1.73 m^2
Sitagliptin-containing products				
Januvia (sitagliptin)	Tablets	Oral	Daily	With or without food Must be dose-adjusted in patients with eGFR < 45 mL/min/1.73 m^2
Janumet (sitagliptin/ metformin HCl)	Tablets	Oral	Two times daily	Individualized based on the patient's current regimen, effectiveness, and tolerability; taken with meals with gradual dose escalation, to reduce the GI side effects due to metformin;

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				tablets must not be split or divided before swallowing Not recommended in patients with an eGFR between 30 and < 45 mL/min/1.73 m^2; contraindicated in patients with an eGFR < 30 mL/min/1.73 m^2 Not recommended in patients with hepatic impairment
Janumet XR (sitagliptin/ metformin HCl extended release)	Tablets	Oral	Daily	Individualized based on the patient's current regimen, effectiveness, and tolerability; taken with a meal preferably in the evening; tablets should be swallowed whole and not split, crushed, or chewed before swallowing Not recommended in patients with an eGFR between 30 and < 45 mL/min/1.73 m^2; contraindicated in patients with an eGFR < 30 mL/min/1.73 m^2 Not recommended in patients with hepatic impairment
Steglujan (sitagliptin/ ertugliflozin)	Tablets	Oral	Daily	Taken in the morning with or without food Volume depletion should be corrected prior to initiation Initiation not recommended if eGFR is between 30 and 60 mL/min/1.73 m^2 Not recommended in patients with an eGFR persistently between 30 and < 60 mL/min/1.73 m^2 Discontinue therapy if eGFR falls below 30 mL/min/1.73 m^2 Not recommended in cases of severe hepatic impairment

See the current prescribing information for full details

CONCLUSION

- The DPP-4 inhibitors or gliptins (alogliptin, linagliptin, saxagliptin, and sitagliptin) are indicated as adjuncts to diet and exercise to improve glycemic control in adults with T2DM. All of the DPP-4 inhibitors are available as combination products with metformin hydrochloride (HCl) and/or extended-release metformin HCl. Alogliptin is also approved as a combination product with the TZD, pioglitazone. Linagliptin, saxagliptin, and sitagliptin are approved as combination products with the SGLT2 inhibitors, empagliflozin, dapagliflozin, and ertugliflozin, respectively.
- The activity of the DPP-4 inhibitors is based on inhibition of the DPP-4 enzyme that mediates physiological degradation of the incretin hormones, glucagon-like peptide 1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP) *(Davis 2014)*.
- Many clinical trials are available comparing DPP-4 inhibitors to placebo and to alternative antihyperglycemic agents, both as monotherapy and in combination regimens. Consistent with treatment guidelines, most trials have evaluated DPP-4 inhibitors not as initial therapy, but as add-on therapy to provide additional glucose control to patients who are not at their goal HbA1c on 1 or more existing therapies *(ADA 2018, Garber et al 2018)*. Most trials evaluated HbA1c as a primary outcome measure, with or without also measuring FPG, PPG, and other metabolic outcomes *(ADA 2018)*.
- DPP-4 inhibitors have modest HbA1c-lowering properties, are weight neutral, and are associated with a low risk of hypoglycemia when not used with insulin secretagogues *(ADA 2018, Garber et al 2018)*. The 4 commercially available DPP-4 inhibitors appear to have similar glycemic efficacy and are well tolerated *(Dungan 2017)*.
- The DPP-4 inhibitors have demonstrated CV safety with respect to MACE in 4 large, DB, PC, randomized CV outcome trials with alogliptin (EXAMINE), saxagliptin (SAVOR-TIMI 53), sitagliptin (TECOS), and linagliptin (CARMELINA). An increased risk of HF with alogliptin and saxagliptin in their respective outcome trials prompted the FDA to add warnings on all of the alogliptin- and saxagliptin-containing products in April 2016 *(Dungan 2017)*. In August 2017, the FDA required similar HF warnings to be added to the labels of the remaining DPP-4 inhibitor-containing products *(Drugs@FDA 2018)*.
- According to current clinical guidelines for the management of T2DM, metformin is the preferred initial pharmacological agent for T2DM. The DPP-4 inhibitors are among the recommended second- or third-line treatment options for patients who are not candidates for metformin or who failed to achieve glycemic goals on metformin therapy. SGLT2 inhibitors and GLP-1 receptor agonists with proven benefit are preferred over DPP-4 inhibitors for patients with T2DM and ASCVD, CKD, or HF *(ADA 2019, Garber et al 2019)*.

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Publication Date: March 26, 2019