Hypoglycemics, Incretin Mimetics/Enhancers
Therapeutic Class Review (TCR)

February 13, 2020

The materials contained herein represent the opinions of the collective authors and editors and should not be construed to be the official representation of any professional organization or group, any state Pharmacy and Therapeutics committee, any state Medicaid Agency, or any other clinical committee. This material is not intended to be relied upon as medical advice for specific medical cases and nothing contained herein should be relied upon by any patient, medical professional or layperson seeking information about a specific course of treatment for a specific medical condition. All readers of this material are responsible for independently obtaining medical advice and guidance from their own physician and/or other medical professional in regard to the best course of treatment for their specific medical condition. This publication, inclusive of all forms contained herein, is intended to be educational in nature and is intended to be used for informational purposes only. Send comments and suggestions to PSTCREditor@magellanhealth.com.

FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indications
Amylin Analogue		
pramlintide (Symlin®)[1]	AstraZeneca	▪ Adjunct therapy in type 1 and type 2 diabetes patients who use mealtime insulin therapy and have failed to achieve desired glucose control despite optimal insulin therapy (with or without concurrent sulfonylurea and/or metformin in type 2 patients)
Dipeptidyl Peptidase-4 (DPP-4) Enzyme Inhibitors		
alogliptin (Nesina®)[2]	Takeda, Perrigo*	▪ Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM)
alogliptin/metformin (Kazano®)[3]	Takeda, Perrigo*	
alogliptin/pioglitazone (Oseni®)[4]	Takeda, Perrigo*	
linagliptin (Tradjenta®)[5]	Boehringer Ingelheim	▪ Adjunct to diet and exercise to improve glycemic control in adults with T2DM
linagliptin/empagliflozin (Glyxambi®)[6]	Boehringer Ingelheim	▪ Adjunct to diet and exercise to improve glycemic control in adults with T2DM ▪ Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with T2DM and established cardiovascular disease (CVD)
linagliptin/empagliflozin/metformin ER (Trijardy™ XR)[7]		
linagliptin/metformin (Jentadueto®)[8]	Boehringer Ingelheim	▪ Adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both linagliptin and metformin is appropriate
linagliptin/metformin ER (Jentadueto® XR)[9]		
saxagliptin (Onglyza®)[10]	AstraZeneca	▪ Adjunct to diet and exercise to improve glycemic control in adults with T2DM
saxagliptin/dapagliflozin (Qtern®)[11]		
saxagliptin/dapagliflozin/metformin ER (Qternmet® XR)[12]		▪ Qternmet XR initiation is intended only for patients currently taking metformin
saxagliptin/metformin ER (Kombiglyze® XR)[13]	AstraZeneca	▪ Adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both saxagliptin and metformin is appropriate
sitagliptin (Januvia®)[14]	Merck Sharp & Dohme	▪ Adjunct to diet and exercise to improve glycemic control in adults with T2DM
sitagliptin/ertugliflozin (Steglujan™)[15]	Merck Sharp & Dohme	▪ Adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both ertugliflozin and sitagliptin is appropriate
sitagliptin/metformin (Janumet®)[16]	Merck Sharp & Dohme	▪ Adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with sitagliptin and metformin is appropriate
sitagliptin/metformin ER (Janumet XR®)[17]	Merck Sharp & Dohme	▪ Adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both sitagliptin and metformin ER is appropriate

ER = extended release

*Available as an authorized generic.

FDA-Approvals Indications (continued)

Drug	Manufacturer	Indications
Glucagon-like Peptide-1 (GLP-1) Receptor Agonists		
dulaglutide (Trulicity®)[18]	Eli Lilly	▪ Adjunct to diet and exercise to improve glycemic control in adults with T2DM
exenatide (Byetta®)[19]	AstraZeneca	▪ Adjunct to diet and exercise to improve glycemic control in adults with T2DM who are taking metformin, a sulfonylurea, thiazolidinedione (TZD), or a combination of metformin and a sulfonylurea or TZD but have not achieved adequate glycemic control ▪ Add-on therapy to insulin glargine, with or without metformin and/or a TZD, in conjunction with diet and exercise for adults with T2DM who are not achieving adequate glycemic control on insulin glargine alone
exenatide ER (Bydureon®, Bydureon® BCise™)[20,21]	AstraZeneca	▪ Adjunct to diet and exercise to improve glycemic control in adults with T2DM
liraglutide (Victoza®)[22]	Novo Nordisk	▪ Adjunct to diet and exercise to improve glycemic control in adult and pediatric patients ≥ 10 years of age with T2DM ▪ Reduce the risk of major adverse cardiovascular events (MACE) in adults with T2DM and established cardiovascular disease (CVD)
liraglutide/insulin degludec (Xultophy®)[23]	Novo Nordisk	▪ Adjunct to diet and exercise to improve glycemic control in adults with T2DM
lixisenatide (Adlyxin®)[24]	Sanofi-Aventis	▪ Adjunct to diet and exercise to improve glycemic control in adults with T2DM
lixisenatide/insulin glargine (Soliqua™)[25]	Sanofi-Aventis	▪ Adjunct to diet and exercise to improve glycemic control in adults with type T2DM
semaglutide (Ozempic®)[26]	Novo Nordisk	▪ Adjunct to diet and exercise to improve glycemic control in adults with T2DM ▪ To reduce the risk of MACE (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) in adults with T2DM and established CVD
semaglutide (Rybelsus®)[27]	Novo Nordisk	▪ Adjunct to diet and exercise to improve glycemic control in adults with T2DM

ER = extended release

Tanzeum® (albiglutide) 30 mg and 50 mg strengths, by GlaxoSmithKline, were discontinued; the anticipated final dates of availability were June 30, 2018 and July 31, 2018, respectively.[28] Product within expiry date may be available.

With the exception of pramlintide (Symlin), these agents should not be used in patients with type 1 diabetes mellitus (T1DM) or diabetic ketoacidosis.

Exenatide (Byetta, Bydureon, Bydureon BCise), liraglutide (Victoza), liraglutide/insulin degludec (Xultophy), lixisenatide (Adlyxin), and lixisenatide/insulin glargine (Soliqua) have not been studied in combination with prandial insulin.

Dulaglutide (Trulicity), exenatide (Byetta), exenatide ER (Bydureon, Bydureon BCise), lixisenatide (Adlyxin), linagliptin (Tradjenta), linagliptin/empagliflozin (Glyxambi), linagliptin/empagliflozin/metformin ER (Trijardy XR), linagliptin/metformin (Jentadueto), linagliptin/metformin ER (Jentadueto XR), lixisenatide/insulin glargine (Soliqua), saxagliptin (Onglyza), saxagliptin/metformin ER (Kombiglyze XR), semaglutide (Ozempic, Rybelsus), sitagliptin (Januvia),

sitagliptin/metformin (Janumet), and sitagliptin/metformin ER (Janumet XR) have not been studied in patients with a history of pancreatitis. Labeling for alogliptin-containing agents (Kazano, Nesina, Oseni) advise that it is unknown if these agents lead to an increased risk of pancreatitis in patients with a history of the condition.

Do not co-administer exenatide (Byetta) and exenatide ER (Bydureon, Bydureon BCise).

Semaglutide oral tablets (Rybelsus) are not recommended as first-line therapy for patients inadequately controlled on diet and exercise.

OVERVIEW

Initial treatment for type 2 diabetes (T2DM) consists of diet, exercise, and metformin, followed by other oral antidiabetic agents and/or exogenous insulin. While this approach improves glycemic control, beta-cell function cannot be completely restored. Available therapies do not correct defects in secretion of other hormones in the glycemic control pathway. In addition to insulin resistance and decreased insulin production, T2DM is characterized by insufficient secretion of the neuroendocrine hormone, amylin, from the pancreatic beta-cells and incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), from the gastrointestinal tract. Novel therapies target these areas and include synthetic hormones, incretin mimetics, and dipeptidyl peptidase-4 (DPP-4) inhibitors.

The American Diabetes Association (ADA) 2020 Standards of Medical Care in Diabetes advises that a reasonable hemoglobin A1c (HbA1c) goal for nonpregnant adults is < 7%; however, a more stringent HbA1c goal of < 6.5% may be considered for select patients (e.g., those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease [CVD]) if this can be achieved without significant hypoglycemia.[29] Less-stringent HbA1c goals (< 8%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain. During pregnancy, the ADA recommends a target HbA1c of 6% (optimal) to < 7% (to prevent hypoglycemia) and notes that more frequent (e.g., monthly) HbA1c monitoring may be required.[30] According to the ADA, selection of an antidiabetic medication should be based on patient-related variables, such as comorbidities, hypoglycemia risk, patient preference, and agent-related variables, such as its effect on body weight, adverse effect profile, and cost.[31] It is generally agreed that metformin, if not contraindicated and if tolerated, is the preferred first-line agent, in addition to lifestyle management, in the treatment of T2DM. If metformin cannot be used, another initial agent could be chosen from the following classes: sulfonylurea (SU), thiazolidinedione (TZD), DPP-4 inhibitor, sodium-glucose cotransporter-2 (SGLT2) inhibitor, GLP-1 receptor agonist, or basal insulin. In patients *without* indicators of high-risk or established atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease (CKD), or heart failure (HF), if initial therapy at maximal tolerated doses does not achieve or maintain the hemoglobin A1c (HbA1c) target after 3 months, another agent from a different class (listed above) should be added. On average, any second agent is typically associated with a further reduction in HbA1c of approximately 1%. In patients *with* indicators of high-risk or established ASCVD, CKD, or HF, the addition of an agent with known cardiovascular (CV), CKD, and/or HF risk reductions, such as a GLP-1 agonist or SGLT2 inhibitor should be considered independent of HbA1c. When ASCVD predominates, a proven GLP-1 agonist or an SGLT2 inhibitor is preferred and when HF or CKD predominates, a proven SLGT2 inhibitors is preferred. For GLP-1

agonists, evidence for reducing CV events is demonstrated for liraglutide, semaglutide, and dulaglutide; exenatide ER resulted in numerically lower major adverse CV events compared to placebo, but the difference was not statistically significant. For SGLT2 inhibitors, empagliflozin (a component of Glyxambi and Trijardy XR), dapagliflozin (a component of Qtern and Qternmet XR), and canagliflozin (not included in this class review) have shown benefit in reducing HF and CKD progression. In addition, insulin degludec (a component of Xultophy) and insulin glargine U-100 (a component of Soliqua) have demonstrated CVD safety. GLP-1 agonists and SGLT2 inhibitors are also preferred when increased body weight is a concern. These 2 classes, as well a DPP-4 inhibitors and TZDs, are beneficial when there is a compelling need to minimize hypoglycemia. In patients newly diagnosed with T2DM with markedly symptomatic and/or elevated blood glucose levels or HbA1c (≥ 10%), basal insulin therapy should be considered, typically with metformin +/- another noninsulin agent. If target HbA1c is still not achieved after 3 months, then addition of a rapid-acting mealtime insulin or a GLP-1 agonist, or change to twice daily premixed insulin should be considered. In older patients at increased risk of hypoglycemia, antidiabetic agents with low risk of hypoglycemia are preferred. For pediatric patients, the ADA recommends a target HbA1c of < 7.5% for all age-groups, although individualization is still supported. In most pediatric patients with T2DM, metformin is preferred as initial treatment in those with HbA1c < 8%. Basal insulin is appropriate as initial therapy if the patient cannot take metformin, or as add-on to initial metformin titration if HbA1c is ≥ 8.5% and the patient is symptomatic, or as add-on if metformin monotherapy is no longer adequate to meet HbA1c goals. If glycemic targets are no longer met with metformin (with or without basal insulin), the GLP-1 agonist liraglutide should be considered in children ≥ 10 years of age.

In 2020, the American Academy of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) updated their algorithm for the management of T2DM, which serves as a supplement to their 2015 clinical practice guidelines for developing a diabetes mellitus comprehensive care plan.[32,33,34] A treatment goal of HbA1c ≤ 6.5% is generally recommended it if can be reached without substantial hypoglycemia or other adverse effects; a goal HbA1c > 6.5% is appropriate if a lower target cannot be achieved without adverse effects. Lifestyle modification, including medically-assisted weight loss, underlies all treatments, as obesity is a risk factor for T2DM and microvascular complications. Choice of antidiabetic therapy should be based on several factors, such as patient status (cardiac, cerebrovascular, renal, obesity), duration of T2DM, hypoglycemia risk, and cost. For patients with HbA1c < 7.5% at entry, lifestyle therapy plus an antidiabetic agent (preferably metformin) is recommended. Patients with an HbA1c ≥ 7.5% should begin with dual therapy with metformin plus another agent. Patients with an HbA1c > 9% and no symptoms may start with dual or triple therapy; patients with an HbA1c > 9% with symptoms should begin insulin therapy with or without other agents. HbA1c should be reassessed every 3 months and failure to improve may warrant additional complementary therapy for optimal glycemic control. The guidelines provide prescribers a hierarchical order of the usage of drugs where metformin is the preferred treatment of choice for monotherapy and first-line agent for dual- and triple-therapy. GLP-1 agonists and SGLT2 inhibitors with proven ASCVD and/or CKD benefits may be preferred, including use as first-line treatment, in patients with those complications. AACE/ACE indicates that GLP-1 agonists have robust HbA1c-lowering properties, are usually associated with weight, lipid, and blood pressure reductions, and have low hypoglycemic risk. AACE/ACE further states liraglutide, empagliflozin (a component of Glyxambi and Trijardy XR), dapagliflozin (a component of Qtern and Qternmet XR), and canagliflozin (not included in this class review) may offer renal and CV benefits, and data for semaglutide and dulaglutide also suggest

associated CV benefit. They also suggest that saxagliptin and alogliptin may be associated with possible CV risk, notably a possible slight increased risk of heart failure; there may be increased risk of bone fractures with canagliflozin; and increased congestive heart failure risk with sulfonylureas, glinides, and insulin. Medications to be used with caution include TZDs and sulfonylureas.

In 2019, the Endocrine Society issued guidelines on screening for and treating diabetes in patients aged ≥ 65 years.[35] They recommend diabetes regimens geared toward minimizing risk for hypoglycemia. The recommended first-line oral pharmacologic treatment is metformin, unless the patient has significant renal impairment or gastrointestinal intolerance. If addition of other agents are required to achieve glycemic goals, agents associated with high risk for hypoglycemia should be avoided (e.g., sulfonylureas and glinides) and insulin should be used sparingly.

In 2017, the American College of Physicians (ACP) updated their recommendations for oral pharmacologic therapy for T2DM.[36] They recommend metformin as first-line therapy and advise that it can be safely used in patients with mild renal impairment and in select patients with moderate impairment. They recommend adding an SU, TZD, SGLT-2 inhibitor, or DPP-4 inhibitor as second-line therapy. In 2018, the ACP developed a statement to guide clinicians in selecting targets for pharmacologic treatment of T2DM, including recommending a goal HbA1c level between 7% and 8% in most patients.[37] In addition, they state that clinicians should consider deintensifying pharmacologic therapy in patients who achieve HbA1c < 6.5%, treat patients to minimize symptoms related to hyperglycemia, and avoid targeting an HbA1c level in patients with a life expectancy < 10 years due to advanced age because the harms outweigh the benefits in this population.

In 2018, the ADA and the European Association for the Study of Diabetes (EASD) updated their 2015 position statement on the management of T2DM.[38] The statement includes a decision cycle for patient-centered glycemic management of T2DM to prevent complications and optimize quality of life. Additional focus is placed on lifestyle management and diabetes self-management education and support. Approaches for weight loss, including lifestyle, medication, and surgical interventions, are recommended for obese patients. When T2DM is not adequately controlled with lifestyle management and metformin, an SGLT2 inhibitor or GLP-1 agonist with proven CV or renal benefit is recommended for patients with ASCVD or CKD or in patients with clinical heart failure and ASCVD (SGLT2 inhibitor preferred). GLP-1 agonists or SGLT2 inhibitors are also recommended when weight loss is key. A DPP-4 inhibitor, GLP-1 agonist, SGLT2 inhibitor, or TZD are recommended when there is compelling need to minimize hypoglycemia. ADA/EASD also states that the first injectable medication recommended is a GLP-1 receptor agonist.

The World Health Organization (WHO) 2018 guidelines regarding treatment intensification in patients with T2DM recommend, as third-line treatment, the addition of a DPP-4 inhibitor, SGLT2 inhibitor, or a TZD to metformin and a sulfonylurea if insulin is unsuitable, such as in persons who live alone who cannot self-inject.[39] In addition, in 2019, the WHO updated their classification of diabetes mellitus based on clinical parameters to identify diabetes subtypes and includes T1DM, T2DM, hybrid forms of diabetes (e.g., slowly evolving immune-mediated, ketosis-prone T2DM), other specific types (e.g., monogenic, drug- or chemical-induced, infection-related), unclassified diabetes, and hyperglycemia first detected during pregnancy.[40]

PHARMACOLOGY[41,42,43,44,45,46,47,48,49,50,51]

Beta cells secrete amylin and insulin in response to food intake. Secretion patterns of amylin in fasting and postprandial situations are similar to that of insulin. In patients with T1DM or T2DM who require insulin, beta cells do not secrete adequate amounts of insulin or amylin in response to food. While insulin aids in uptake of blood glucose by muscle, pramlintide (Symlin), a synthetic analogue of amylin, affects the rate of glucose appearance in the blood by several mechanisms. Pramlintide slows gastric emptying, suppresses glucagon secretion, and centrally modulates appetite.

The incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. Incretins are released by the intestines throughout the day and their levels increase in response to meals. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from the pancreatic beta cells. GLP-1 also slows gastric emptying and lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. GIP and GLP-1 are rapidly inactivated by the DPP-4 enzyme.

The GLP-1 agonist agents, dulaglutide (Trulicity), exenatide (Byetta, Bydureon, Bydureon BCise), liraglutide (Victoza), lixisenatide (Adlyxin), and semaglutide (Ozempic, Rybelsus) enhance glucose-dependent insulin secretion by the beta cell, suppress inappropriately elevated glucagon secretion, and slow gastric emptying.

Liraglutide/insulin degludec (Xultophy) and lixisenatide/insulin glargine (Soliqua) combine a GLP-1 receptor agonist with a long-acting insulin analogue. Insulin lowers blood glucose levels by stimulating peripheral glucose uptake by skeletal muscle and fat, and by inhibiting gluconeogenesis. Insulin also inhibits lipolysis in the adipocyte, inhibits proteolysis, and enhances protein synthesis.

Alogliptin (Nesina), linagliptin (Tradjenta), saxagliptin (Onglyza), and sitagliptin (Januvia) are DPP-4 enzyme inhibitors. Blocking the DPP-4 enzyme slows inactivation of GLP-1 and GIP, and prolongs the action of the incretins. DPP-4 inhibition increases insulin secretion and reduces glucagon secretion by preventing the inactivation of GLP-1, thereby lowering glucose levels.

Alogliptin/metformin (Kazano), linagliptin/metformin (Jentadueto), saxagliptin/metformin ER (Kombiglyze XR), sitagliptin/metformin (Janumet), and sitagliptin/metformin ER (Janumet XR) combine a DPP-4 enzyme inhibitor with metformin. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Alogliptin/pioglitazone (Oseni) combines a DPP-4 enzyme inhibitor with a TZD. Pioglitazone is a peroxisome proliferator-activated receptor-gamma agonist that improves insulin sensitivity in muscle and adipose tissue and inhibits hepatic gluconeogenesis. Linagliptin/empagliflozin (Glyxambi), saxagliptin/dapagliflozin (Qtern), and sitagliptin/ertugliflozin (Steglujan) combine a DPP-4 enzyme inhibitor with a sodium-glucose cotransporter-2 (SGLT2) inhibitor that increases urinary glucose excretion by inhibiting SGLT2, the major transporter responsible for the reabsorption of filtered glucose from the kidney.

Linagliptin/empagliflozin/metformin ER (Trijardy XR) and saxagliptin/dapagliflozin/metformin ER (Qternmet XR) are triple combination products containing a DPP-4 inhibitor, an SGLT2 inhibitor, and extended-release metformin.

PHARMACOKINETICS[52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79]

Drug	Peak (hrs)	Half-life (hrs)	Metabolism	Excretion
Amylin Analogue				
pramlintide (Symlin)	0.33	0.8	Primarily by kidneys to deslys pramlintide (active metabolite)	--
DPP-4 Enzyme Inhibitors Containing Products				
alogliptin (Nesina)	1-2	21	Active metabolite: N-demethylated alogliptin < 1% of the parent compound	Urine: 76% Feces: 13%
saxagliptin (Onglyza)	2 (parent drug) 4 (active metabolite)	2.5 (parent drug) 3.1 (active metabolite)	CYP3A4/5; active metabolite – 5-hydroxy saxagliptin which is one-half as potent as saxagliptin	Urine: 75% Feces: 22%
sitagliptin (Januvia)	1-4	12.4	Primarily by CYP3A4 (minor)	Urine: 87% Feces 13%
linagliptin (Tradjenta)	1.5	12	90% unchanged, no active metabolite	Urine: 5% Feces: 80%
dapagliflozin	2 (fasting) 3 (high-fat meal)	12.9	Primarily via UGT1A9; minor CYP-mediated	Urine: 75% Feces: 21%
empagliflozin	1.5	12.4	hepatic (O-glucuronidation via UGT1A3 & 1A8, & 1A9)	Urine: 54.4% Feces: 41.2%
ertugliflozin	1 to 4	12.4	hepatic (O-glucuronidation via UGT1A9 & 2B7)	Urine 50.2% Feces: 40.9%
metformin	4-8	6.2	None	Excreted unchanged in the urine
pioglitazone	2	3-7 (parent drug) 16-24 (metabolites)	Extensive hydroxylation and oxidation; 2 major active metabolites	Urine: 15%-30% Feces: majority
GLP-1 Receptor Agonists				
dulaglutide (Trulicity)	24-72	5 days	Protein catabolism	nr
exenatide (Byetta)	2.1	2.4	Predominantly by the kidneys	Predominantly by the kidneys
exenatide ER (Bydureon, Bydureon BCise)	Peak 1: 2 weeks Peak 2: 6-7 Weeks	4 days	Predominantly by the kidneys	Predominantly by the kidneys

Pharmacokinetics (continued)

Drug	Peak (hrs)	Half-life (hrs)	Metabolism	Excretion
GLP-1 Receptor Agonists *(continued)*				
liraglutide (Victoza)	8-12	13	Metabolized in a similar manner to large proteins without a specific organ as a major route of elimination.	Minimally excreted in urine (6%) and feces (5%) as metabolites
lixisenatide (Adlyxin)	1-3.5	3	Glomerular filtration and proteolytic degradation	Predominantly by the kidneys
insulin degludec (component of Xultophy)	9	25	Inactive metabolites	nr
insulin glargine (component of Soliqua)	5 (no actual peak as insulin glargine is released slowly over 24 hours)	nr	Partly metabolized at the carboxyl terminus of the B chain	nr
semaglutide (Ozempic)	1-3 days	7 days	Proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid sidechain	Primarily via urine and feces
semaglutide (Rybelsus)	1			

In bioequivalence studies, alogliptin/metformin (Kazano), alogliptin/pioglitazone (Oseni), linagliptin/empagliflozin (Glyxambi), linagliptin/empagliflozin/metformin ER (Trijardy XR), linagliptin/metformin (Jentadueto), linagliptin/metformin ER (Jentadueto XR), saxagliptin/metformin ER (Kombiglyze XR), sitagliptin/metformin (Janumet), and sitagliptin/ metformin ER (Janumet XR) were found to be bioequivalent to the single agents administered together. The combination of lixisenatide and insulin glargine (Soliqua) does not impact the pharmacodynamics of insulin glargine; it is not known if the combination has an impact on lixisenatide pharmacodynamics. Overall, the pharmacokinetics of insulin degludec and liraglutide (Xultophy) were not affected in a clinically relevant manner when administered as a combination product. In a drug-drug interaction study between dapagliflozin and saxagliptin (components of Qtern), a lack of pharmacokinetic interaction between the agents was demonstrated. In addition, there were not clinically important changes in the overall pharmacokinetics of saxagliptin, dapagliflozin, and metformin when administered in combination as Qternmet XR. Coadministration of single doses of ertugliflozin (15 mg) and sitagliptin (100 mg) did not meaningfully alter the pharmacokinetics of ertugliflozin; the effects on sitagliptin were not reported in the Steglujan labeling.

Exenatide (Byetta) is considered to be a short-acting GLP-1 receptor agonist and is dosed twice daily.[80] The exenatide ER formulations (Bydureon, Bydureon BCise) release exenatide from microspheres over a period of about 10 weeks and allows for once weekly dosing. Dulaglutide (Trulicity), and injectable semaglutide (Ozempic) have a longer half-life due, at least in part, to a decreased DPP-4 degradation in the body, making them appropriate for once weekly dosing.[81] The longer-acting agents have a stronger effect on fasting glucose levels, while shorter-acting agents primarily lower postprandial blood glucose levels through inhibition of gastric emptying.[82]

While the injectable GLP-1 agonists have limited gastrointestinal (GI) epithelium permeability, oral semaglutide (Rybelsus) is co-formulated with an absorption enhancer, salcaprozate sodium (SNAC), which facilitates semaglutide across the gastric epithelium. Absolute bioavailability is estimated to be 0.4% to 1%. The time to maximum serum concentration (T_{max}) is achieved in approximately 1 hour. Steady-state exposure is reached in 4 to 5 weeks.

Administration of DPP-4 inhibitors, including combination products, with food had no clinically relevant effect on drug exposure. In general, DPP-4 inhibitors that are combined with metformin should be taken with food to reduce gastrointestinal side effects associated with metformin.

Insulin degludec and insulin glargine are long-acting insulins. Duration of action of insulin degludec beyond 42 hours has been demonstrated; duration for insulin glargine U-100 is approximately 24 hours.

CONTRAINDICATIONS/WARNINGS[83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109]

Each product in this class is contraindicated in patients who have a known hypersensitivity to any of its components. Severe reactions, including angioedema, have been reported with the GLP-1 agonists dulaglutide (Trulicity), exenatide ER (Bydureon, Bydureon BCise), and liraglutide (Victoza).

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with any antidiabetic agent, except empagliflozin (Jardiance), linagliptin/empagliflozin (Glyxambi) liraglutide (Victoza), and lixisenatide (Adlyxin). Data from 3 CVD outcome randomized controlled trials with alogliptin, linagliptin, saxagliptin, and sitagliptin report no harm but did not show any benefit on major CVD events.[110,111,112] A modest but significant increased risk of hospitalization for heart failure (HF) was observed with saxagliptin and with alogliptin (only in subjects with no history of HF), but not with sitagliptin. Risk and benefit of linagliptin- and sitagliptin-containing products (Tradjenta, Jentadueto, Jentadueto XR, Glyxambi, Trijardy XR, Januvia, Janumet, Janumet XR, Steglujan) should be considered when initiating treatment in patients at risk for HF. If HF develops while on therapy, evaluate and manage appropriately.

In March 2013, the FDA published an alert stating that patients with T2DM treated with DPP-4 inhibitors or GLP-1 agonists may be at increased risk of pancreatitis and pre-cancerous cellular changes (pancreatic duct metaplasia).[113] This warning is based on examination of a small number of pancreatic tissue specimens taken from patients after death due to unspecified causes. Subsequently, in March 2014, based on review of toxicology studies that showed no incretin-associated adverse effects on the pancreas, the FDA and European Medicines Agency (EMA) announced that they have not reached a final conclusion about a causal relationship between the use of incretin-based drugs and pancreatitis or pancreatic cancer.[114] Both agencies continue to investigate this safety signal.

A study published in the Journal of the American Medical Association (JAMA) Internal Medicine concluded that treatment with the GLP-1 based therapies, sitagliptin and exenatide, both with current (within 30 days) and recent use (> 30 days and < 2 years) are associated with an increased risk of hospitalization for acute pancreatitis (adjusted odds ratio [OR], 2.24; 95% confidence interval [CI], 1.36 to 3.68) and (OR, 2.01 [95% CI, 1.37 to 3.18]), respectively.[115] In a joint response to this article, the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) said the new findings should not change treatment in patients with diabetes.[116]

In July/August 2013, the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) issued a consensus statement on diabetes and cancer to review factors associated with cancer development in people with obesity and diabetes, and to discuss the possible cancer risk of antihyperglycemic medications.[117] According to the consensus, there currently is insufficient evidence of a definitive link between incretin diabetes medications and an increased risk of cancer. The time generally needed for the clinical appearance of a pancreatic neoplasm following an initiating event is on the order of 12 years, and another decade usually is required before metastatic disease develops. In addition, current evidence is primarily based on animal research and epidemiologic studies. AACE/ACE was unable to definitively rule out the possibility that exposure to antidiabetic drugs themselves could act as an initiating event or could be tumor-promoting. Rather than focusing on the potential hazards of specific antidiabetic agents, the consensus statement emphasizes the importance of better managing obesity which has been linked with various malignancies, including breast, endometrial, pancreatic, and colorectal cancers.

In February 2015, in an effort to reduce the transmission risk of serious infections, such as human immunodeficiency virus (HIV) and hepatitis, through sharing of multidose diabetes pen devices, the FDA required the addition of warnings to the product labels advising against the sharing of multi-dose pens.[118] Agents in this review that utilize a multidose pen device include pramlintide (Symlin) and the GLP-1 agonists.

Exposure to stressors such as fever, trauma, infection, or surgery or change in regular physical activity may necessitate a change in antidiabetic treatment. Patients should seek medical advice.

Amylin Analogue

Pramlintide is contraindicated in patients with gastroparesis or hypoglycemia unawareness. Pramlintide also carries a boxed warning for severe hypoglycemia associated with concomitant use of insulin.

Pramlintide should only be considered in patients who have failed to achieve adequate glycemic control on insulin. Patients who are not candidates for pramlintide include patients with HbA1c > 9% or who require use of drugs that stimulate gastrointestinal (GI) motility.

DPP-4 Enzyme Inhibitors

The combination products linagliptin/empagliflozin (Glyxambi), linagliptin/empagliflozin/metformin ER (Trijardy XR), saxagliptin/dapagliflozin (Qtern), saxagliptin/dapagliflozin/metformin ER (Qternmet XR), and sitagliptin/ertugliflozin (Steglujan) are contraindicated in patients with severe renal impairment, end-stage renal disease (ESRD), or dialysis due to the SGLT2 inhibitor component. Linagliptin/empagliflozin/metformin ER, saxagliptin/dapagliflozin, and saxagliptin/dapagliflozin/metformin ER also should not be used in patients with moderate renal impairment; do not initiate in patients with estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73m^2. Renal function should be evaluated prior to initiating therapy and periodically thereafter.

Saxagliptin/metformin ER (Kombiglyze XR) is contraindicated in patient with severe renal impairment (eGFR < 30 mL/min/1.73m^2), and initiation of the product is not recommended with eGFR between 30 and 45 mL/min/1.73m^2. If eGFR falls below 45 mL/min/1.73m^2 during saxagliptin/metformin therapy, assess the benefit and risk of continuing therapy.

There have been post-marketing reports of worsening renal function, including acute renal failure, sometimes requiring dialysis, with sitagliptin use. Renal injury may resolve with supportive care and discontinuation of sitagliptin. Consideration can be given to cautiously restarting sitagliptin if another etiology is deemed likely to have precipitated the altered renal function. Do not restart a combination product containing sitagliptin/metformin in the presence of altered renal function. Renal function should be assessed before and during sitagliptin therapy.

There have been post-marketing reports of worsening renal function, including acute renal failure (sometimes requiring hospitalization) and dialysis, with use of SGLT2 inhibitors (a component in Qtern, Qternmet XR, Glyxambi, Trijardy XR, and Steglujan). In addition, increases in serum creatinine and decreases in eGFR may occur when starting therapy, specifically in the elderly or patients with renal impairment. Evaluate renal function prior to starting therapy. Consider temporary discontinuation with reduced oral intake or fluid losses.

DPP-4 inhibitors have been associated with serious hypersensitivity reactions in post-marketing reports. Reactions varied in severity and include anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, exfoliative skin conditions, such as Stevens-Johnson syndrome (SJS), and elevations in hepatic enzymes. Onset of reactions occurred after the initial dose to within the first 3 months after starting treatment. DPP-4 therapy should be discontinued immediately and alternative antidiabetic therapy initiated if a hypersensitivity reaction is suspected. Assess the patient for other potential causes of the suspected reaction and institute appropriate treatment and monitor accordingly.

There have been post-marketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, associated with DPP-4 inhibitor use. If pancreatitis occurs, promptly discontinue therapy. It is unknown if patients receiving DPP-4 inhibitors with a prior history of pancreatitis are at an increased risk for development of pancreatitis. In a cardiovascular (CV) outcomes study, pancreatitis was reported in 0.2% of patients treated with saxagliptin compared to 0.1% with placebo; a greater percentage of patients in the saxagliptin group had pre-existing risk factors for pancreatitis (88% versus 100%). Another study reported acute pancreatitis in 9 (0.3%) patients treated with linagliptin, including 2 with fatal outcomes, compared to 5 cases (0.5%) that occurred with placebo.

The use of DPP-4 inhibitors or the SGLT2 inhibitors, dapagliflozin, empagliflozin, or ertugliflozin, available in a fixed-dose tablet with a DPP-4 inhibitor (Qtern, Qternmet XR, Glyxambi, Trijardy XR, Steglujan), in combination with an insulin secretagogue or with insulin has been associated with a higher rate of hypoglycemia compared to placebo. A lower dose of the insulin secretagogue or insulin may be required to lower the risk of hypoglycemia when these agents are used together.

The EXAMINE study showed that the primary endpoint (CV death, nonfatal MI, and nonfatal stroke) occurred at similar rates for alogliptin and placebo in 5,380 patients with diabetes and an acute MI/unstable angina requiring hospitalization.[119] The SAVOR TIMI-53 study evaluated CV outcomes with saxagliptin in patients (n=16,492) with T2DM, an eGFR ≤ 50 mL/minute) and a history of or at risk for CV events.[120] Saxagliptin had no effect on the composite of CV death, myocardial infarction (MI), or ischemic stroke, but was associated with an increased rate of hospitalization for heart failure (HF). The results of the SAVOR-TIMI 53 CV outcomes trial prompted the FDA to investigate the possible association between DPP-4 inhibitors and HF.[121] The FDA's review concluded that medicines containing saxagliptin or alogliptin may increase the risk of HF, particularly in patients with pre-existing cardiac or

renal disease.[122] Both agents were associated with increased rates of hospitalization for HF compared to placebo (saxagliptin 3.5% versus 2.8%, respectively; alogliptin 3.9% versus 3.3%, respectively). Labeling for sitagliptin/ertugliflozin (Steglujan) advises to consider the risks and benefits of therapy prior to starting treatment in patients at risk for heart failure.

Alogliptin/pioglitazone (Oseni) is not recommended in patients with symptomatic HF as thiazolidinediones (TZDs) can cause fluid retention. Boxed warnings for TZD-containing products include cause or exacerbation of congestive HF; therefore, patients should be monitored for signs and symptoms of HF. Initiation of alogliptin/pioglitazone in patients with established New York Heart Association (NYHA) Class III or IV HF is contraindicated.

A national commercially-insured US database was used to evaluate the association of sitagliptin and HF.[123] In the analysis, 7,620 patients were identified with incident HF and also having T2DM. Subjects subsequently using sitagliptin were compared with those not using sitagliptin in the 90 days before the occurrence of all-cause hospital admission or death. The analysis found that there was no increased risk of all-cause hospitalization or death associated with sitagliptin use; however, there was an increased risk of HF-related hospitalization among this cohort. In addition, the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) evaluated the impact of sitagliptin on CV risk in 14,671 patients with T2DM and CV disease.[124] After a median of 3 years, sitagliptin did not result in an increased risk of CV events, including hospitalization for HF, as measured by the primary outcome of a composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina.

The FDA identified a potential increased risk of ketoacidosis and urosepsis in patients taking SGLT2 inhibitor, including products that contain dapagliflozin, empagliflozin, and ertugliflozin.[125] Fatal cases of ketoacidosis have been reported in patients taking dapagliflozin. Prior to starting SGLT2 inhibitor treatment, consider predisposing factors for ketoacidosis (pancreatic insulin deficiency, caloric restriction, alcohol abuse. Patients should seek immediate medical attention if they experience difficulty breathing, nausea, vomiting, abdominal pain, confusion, and unusual fatigue or sleepiness. Dapagliflozin-, empagliflozin-, or ertugliflozin-containing products should be discontinued if acidosis is confirmed.

Symptomatic hypotension can occur after starting dapagliflozin, empagliflozin, or ertugliflozin due to osmotic diuresis leading to intravascular volume contraction. This is particularly seen in patients with impaired renal function (eGFR < 60 mL/min/1.73 m^2), elderly patients, patients with low systolic blood pressure, and patients on diuretics or drugs which interfere with the renin-angiotensin-aldosterone system. Volume status should be assessed and corrected prior to starting empagliflozin therapy and monitored thereafter.

Products containing dapagliflozin, empagliflozin, or ertugliflozin (components of Qtern and Qternmet XR, Glyxambi and Trijardy XR, and Steglujan, respectively) increase the risk for urinary tract infections and genital mycotic infections and may increase low-density lipoprotein cholesterol (LDL-C) levels. Monitor and treat patients appropriately.

In 2016, an updated FDA review confirmed preclinical and clinical trial data and results from an observational study suggest an increased risk of bladder cancer in pioglitazone users. The observational data further suggest that the risk increases with duration of use. Do not use alogliptin/pioglitazone (Oseni) in patients with active bladder cancer. Use caution when using in patients with a prior history of bladder cancer.

Fatal and non-fatal hepatic failure have been reported in patients taking alogliptin and pioglitazone. It is recommended that a liver function test be performed prior to beginning alogliptin (Nesina, Kazano, Oseni) therapy, particularly if prescribed with pioglitazone; therapy may be started with caution, if abnormal test results are produced.

Combination products containing metformin (Janumet, Janumet XR, Jentadueto, Jentadueto XR, Kazano, Kombiglyze XR, Qternmet XR, Trijardy XR) carry a boxed warning for lactic acidosis due to the accumulation of the metformin component. In addition, these agents are contraindicated in patients with acute or chronic metabolic acidosis, including diabetic ketoacidosis. Post-marketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The risk increases with conditions such as age ≥ 65 years, radiological studies with contrast, surgery, hypoxic state, excess alcohol intake, concomitant use of carbonic anhydrase inhibitors (topiramate), and hepatic insufficiency. Symptoms of lactic acidosis include malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include blood lactate, anion gap acidosis, lactate/pyruvate ratio, and metformin plasma level > 5 mcg/mL. If acidosis is suspected, DPP-4 inhibitor/metformin therapy should be discontinued and the patient hospitalized immediately; prompt hemodialysis is recommended as metformin is substantially secreted by the kidney. Metformin is contraindicated in patients with an eGFR < 30 mL/min/1.73m^2. In addition, impaired hepatic function has been associated with some cases of lactic acidosis; metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients treated with metformin-containing regimens should be advised to avoid excessive alcohol intake.

Product labeling advises to temporarily discontinue linagliptin/empagliflozin (Glyxambi), linagliptin/empagliflozin/metformin ER (Trijardy XR), and saxagliptin/dapagliflozin (Qtern) for at least 3 days and sitagliptin/ertugliflozin (Steglujan) for at least 4 days prior to a scheduled surgery. Temporary discontinuation can also be considered for other clinical situations that may lead to ketoacidosis.

Use of metformin-containing products should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Metformin may lower vitamin B12 levels. Monitor hematologic parameters annually. In addition, the potential exists for unintended pregnancy in premenopausal anovulatory women, since metformin may cause ovulation in these women.

There have been reports of incompletely dissolved sitagliptin/metformin ER (Janumet XR) tablets and linagliptin/metformin ER (Jentadueto XR) being eliminated in the feces.[126] It is not known if tablets eliminated contain drug. If a patient reports repeated tablets in stool, assess adequacy of glycemic control.

In August 2015, a safety communication by the FDA warned that DPP-4 inhibitors may cause joint pain that can be severe and disabling.[127] The FDA advises that patients should contact their health care provider (HCP) immediately if severe or persistent joint pain occurs; HCPs should consider stopping DPP-4 inhibitor therapy.

In clinical studies, incidence of bone fracture in females was approximately double for pioglitazone versus for placebo (5.1% versus 2.5%) after the first year of therapy; a similar incidence of fractures was not seen in men.

An increased risk of lower limb amputation has been observed with another SGLT2 inhibitor, not included in this therapeutic class review. Across 7 clinical trials, non-traumatic lower limb amputations were reported in 3 (0.2%) patients in the ertugliflozin 5 mg group, 8 (0.5%) patients in the ertugliflozin 15 mg group, and 1 (0.1%) patient in the comparator group. A causal relationship has not been definitively established. Patient history and predisposing factors to amputations should be considered prior to initiating treatment with sitagliptin/ertugliflozin (Steglujan).

Post-marketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. The condition generally resolved with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor.

There have been post-marketing reports of severe and disabling arthralgia beginning days to years after initiating DPP-4 inhibitor therapy. Relief of symptoms occurred upon discontinuation.

In August 2018, the FDA alerted the public of reports of Fournier's gangrene (FG), a rare, but serious, necrotizing fasciitis of the genitals and surrounding area, associated with SGLT2 inhibitors-containing product (Glyxambi, Qtern, Steglujan).[128] Since the approval of SGLT2 inhibitors in 2013, a total of 12 cases of FG have been confirmed within several months of starting therapy. In all cases, the SLGT2 inhibitor was stopped and surgery required. Symptoms include tenderness, redness, or swelling in the peri-genital area, body temperature > 100.4° F, or general malaise. FG can progress quickly and become life-threatening; therefore, it is important that patients on SGLT2 inhibitor therapy seek immediate medical attention if they experience any of these symptoms. If FG is suspected, a broad-spectrum antibiotic should be started, the SGLT2 inhibitor should be stopped, and appropriate alternative antidiabetic agent should be initiated. A warning regarding risk of FG was added to the labeling of all SGLT2 inhibitors-containing products.

GLP-1 Receptor Agonists

GLP-1 receptor agonists are not a substitute for insulin therapy.

Dulaglutide (Trulicity), exenatide ER (Bydureon, Bydureon BCise), liraglutide (Victoza), liraglutide/insulin glargine (Xultophy), and semaglutide (Ozempic, Rybelsus) are contraindicated in patients with either a personal or family history of medullary thyroid carcinoma (MTC) and in patients with multiple endocrine neoplasia syndrome type 2 (MEN 2) and carry a boxed warning regarding the risk of MTC and MEN 2. Clinically relevant doses of GLP-1 receptor agonists have demonstrated dose-related and treatment-duration-dependent increases in incidence of thyroid C-cell tumors in nonclinical studies in rodents; however, it is unknown whether these drugs are associated with thyroid C-cell tumors, including MTC, in humans. Patients should be advised of MTC risk and informed of symptoms of thyroid tumors. The value of routine serum calcitonin or thyroid ultrasound monitoring is uncertain.

Acute pancreatitis has been reported in association with dulaglutide and semaglutide (Ozempic, Rybelsus) in clinical trials. If pancreatitis is suspected, therapy should be promptly discontinued and, if confirmed, an alternative antidiabetic agents should be used. Post-marketing reports of pancreatitis, including fatal and non-fatal hemorrhagic necrotizing pancreatitis, have occurred with exenatide,

exenatide ER, liraglutide, and lixisenatide use. After therapy initiation with any of the agents, patients should be observed for symptoms of pancreatitis and the drug discontinued if pancreatitis is suspected. The drug should not be restarted if pancreatitis is confirmed.

Use of GLP-1 agonists has been associated with gastrointestinal adverse reactions. Labeling for all GLP-1 receptor agonists, except semaglutide (oral and injectable), state that their use has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis; therefore, they are not recommended for patients with severe gastrointestinal disease. Exenatide (Byetta), liraglutide, lixisenatide, and injectable semaglutide dosages are titrated during the first 1 to 4 weeks (depending on the product) of therapy to reduce gastrointestinal symptoms. The starting dose for oral semaglutide (3 mg once daily) is given for the first 30 days of treatment, then the dose is increased to 7 mg once daily. Additional increases can be made after 30 days of the 7 mg daily dosing.

Acute events of gallbladder disease (e.g., cholelithiasis, cholecystitis) have been reported with GLP-1 agonists, including with exenatide ER (Bydureon; EXSCEL clinical trial). If cholelithiasis is suspected, gallbladder studies and appropriate follow-up are recommended.

Acute renal failure and worsening of chronic renal failure, which may warrant hemodialysis, have been reported post-marketing with GLP-1 receptor agonists. Some reports have been in patients without known underlying renal disease. Some of the events occurred in patients receiving 1 or more medications known to affect renal function or hydration status. Nausea, vomiting, diarrhea, or dehydration was reported by the majority of patients who experienced acute renal failure or worsening of chronic renal failure. Since these gastrointestinal reactions may worsen renal function, caution should be used with initiating or increasing doses of these agents in patients with renal impairment. Reversibility of altered renal function has been observed with supportive treatment and discontinuation of potentially causative agents. Exenatide (Byetta) is not recommended in patients with severe renal impairment (CrCl < 30 mL/min) or ESRD, and should be used cautiously in renal transplant recipients. Exenatide ER (Bydureon, Bydureon Bcise) labeling has been updated to advise that an increased exposure to exenatide has been found in patients with mild or moderate renal impairment and may lead to nausea and vomiting with transient hypovolemia and may worsen renal function. Exenatide is not recommended in patients with eGFR < 45 mL/min/1.73 m2 or ESRD. In the LEADER cardiovascular outcomes trial, no overall differences in safety or efficacy of liraglutide (Victoza) were seen in patients with any level of renal impairment compared to those with normal renal function. There is limited experience with liraglutide in patients with ESRD.

Hypersensitivity reactions, including anaphylaxis and angioedema, have been reported with GLP-1 agonist use. If hypersensitivity reactions occur, discontinue GLP-1 agonist therapy and promptly seek medical advice.

Glucose lowering with GLP-1 agonists is not associated with an inherently high risk of hypoglycemia.129,130,131 However, when GLP-1 agonists are used in combination with an insulin secretagogue or insulin, patients may be at increased risk for hypoglycemic episodes. Reduced dosage of the insulin secretagogue or insulin may be required. However, the combination products, liraglutide/insulin degludec and lixisenatide/insulin glargine, are contraindicated during episodes of hypoglycemia, due to their insulin component. In pediatric patients ≥ 10 years of age with T2DM, the hypoglycemia risk was higher with liraglutide, regardless of concurrent antidiabetic therapies.

Patients may develop anti-exenatide antibodies following treatment with exenatide. In most patients, titers diminish over time. For those whose titers increase over time, glycemic response to exenatide may be attenuated. In clinical studies, approximately 10% of subjects on liraglutide formed antibodies to the drug; however, efficacy and safety were not affected. In clinical studies, 70% of lixisenatide-treated patients developed antibodies to lixisenatide at week 24 of therapy. An increased incidence of allergic and injection site reactions may occur in antibody positive patients. A subset of patients with the highest antibody concentration to lixisenatide (2.4%) reported reduced glycemic response. No dulaglutide anti-drug antibodies were found in clinical pharmacology studies.132 Out of 11 patients who developed anti-bodies to liraglutide, none developed neutralizing antibodies, and 5 developed cross-reacting antibodies against native GLP-1. The potential exists for the development of antibodies to insulin. Across clinical trials, 32 patients (1%) of patients treated with semaglutide developed anti-drug antibodies; of these, 19 patients developed antibodies cross-reacting with native GLP-1. Their neutralizing activities are not known.

In a 2-year trial, diabetic retinopathy complications were reported more often in patients treated with injectable semaglutide (3%) than those treated with placebo (1.8%), and the risk was greater in patients with a history of diabetic retinopathy at baseline. In a pooled analysis, diabetic retinopathy related adverse reactions were reported in 4.2% of patients on oral semaglutide and 3.8% with the comparator). While temporary worsening of diabetic retinopathy has been linked to rapid improvement in glucose control, patients with a history of diabetic retinopathy should be monitored closely.

Liraglutide/insulin degludec and lixisenatide/insulin glargine may lead to hypokalemia, due to the insulin component. Potassium levels should be monitored in at risk patients.

Liraglutide/insulin degludec and lixisenatide/insulin glargine should not be used in combination with other GLP-1 receptor-containing products. Therapy with the GLP-1 agonist component or basal insulin should be stopped prior to initiating the combination product. In addition, concomitant use with a TZD can lead to dose-related fluid retention, which can in turn exacerbate HF.

Repeated insulin injections into areas of lipodystrophy or localized cutaneous amyloidosis have been reported to result in hyperglycemia, and a sudden change in injection site to unaffected areas has been reported to result in hypoglycemia. Patients should be aware to rotate injection sites.

Risk Evaluation and Mitigation Strategies (REMS)

The REMS requirements for dulaglutide (Trulicity), exenatide ER (Byetta), liraglutide (Victoza), and liraglutide/insulin degludec (Xultophy) were eliminated since the FDA determined that the program goals were met. Medication Guides are maintained for all incretin mimetic agents regardless of REMS requirements. The REMS requirement for pramlintide (Symlin) was eliminated.

DRUG INTERACTIONS[133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158]

Beta-blockers and clonidine may mask the signs and symptoms of hypoglycemia.

Some medications can predispose patients to hyperglycemia and may lead to loss of glycemic control. These medications include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel

blockers, and isoniazid. Patients should be closely observed for changes in glycemic control when starting or stopping these medications.

Amylin Analogue

Pramlintide (Symlin) may delay the absorption of concomitantly-administered oral medications. When rapid onset of an oral medication is critical, the drug should be administered at least 1 hour before or 2 hours after pramlintide. Pramlintide should also not be prescribed for patients taking other medications that alter gastric motility or absorption of nutrients.

DPP-4 Enzyme Inhibitors

Alogliptin (Nesina) is primarily renally excreted. No significant drug-drug interactions were observed with the CYP-substrates or inhibitors tested, or with renally excreted drugs. In patients on alogliptin/pioglitazone (Oseni), the maximum recommended dose of pioglitazone is 15 mg daily if used in combination with strong CYP2C8 inhibitors (e.g., gemfibrozil). Likewise, the maximum recommended daily dose of 45 mg for pioglitazone is recommended if co-administered with a strong CYP2C8 inducer (e.g., rifampin).

Concurrent use of topiramate and pioglitazone, a component of Oseni, may decrease exposure to pioglitazone and its active metabolites. Glycemic controlled should be monitored.

Concomitant use of linagliptin (Tradjenta, Glyxambi, Jentadueto, Jentadueto XR, Trijardy XR) with a strong p-glycoprotein or CYP3A4 inducer, such as rifampin, may decrease linagliptin exposure to subtherapeutic levels; use of an alternative treatment is strongly recommended. A lower dose of insulin may be required to reduce the risk of hypoglycemia when used in combination with linagliptin.

Saxagliptin (Kombiglyze XR, Onglyza, Qtern, Qternmet XR) is metabolized primarily by the cytochrome P450 3A4/5 (CYP3A4/5) enzymes. Drugs that are strong inhibitors of these enzymes can significantly increase the exposure of saxagliptin. The dose for saxagliptin should be limited to 2.5 mg when co-administered with strong CYP3A4/5 inhibitors, such as ketoconazole, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin. Dosage adjustment of saxagliptin is not recommended when given concomitantly with drugs that are inducers or moderate inhibitors of the CYP3A4/5 enzyme. Saxagliptin does not significantly alter the pharmacokinetics of drugs that are metabolized by CYP3A4/5 and other cytochrome P450 enzyme systems; studies were performed with metformin, glyburide, pioglitazone, digoxin, diltiazem, and ketoconazole. Saxagliptin/dapagliflozin (Qtern) should not be coadministered with strong CYP3A4/5 inhibitors.

Sitagliptin (Januvia, Janumet/XR, Steglujan) is metabolized via the CYP450 enzymes but has low likelihood for causing drug interactions. Sitagliptin-containing products may cause a slight increase exposure of digoxin when given concurrently. Patients receiving digoxin should be monitored appropriately; however, no dosage adjustment of either agent is recommended.

Co-administration of dapagliflozin, empagliflozin, or ertugliflozin with diuretics can increase the potential for volume depletion and use with insulin or insulin secretagogues can increase the risk for hypoglycemia. In addition, monitoring glycemic control with urine glucose tests or with 1,5-AG assay is not recommended in patients taking empagliflozin as these methods will lead to inaccurate results.

Concurrent use of metformin-containing products (Janumet, Janumet XR, Jentadueto, Jentadueto XR, Trijardy XR, Kazano, Kombiglyze XR, Qternmet XR) and carbonic anhydrase inhibitors should be used with caution since it could cause metabolic acidosis. Concurrent use of drugs that interfere with common renal transport systems (e.g., amiloride, cimetidine, dolutegravir, morphine, procainamide, ranolazine, quinidine, triamterene) have the potential for interaction with metformin. Consider benefit and risk of concomitant use. Careful patient monitoring and/or dose adjustment of metformin-containing DPP4-inhibitors should be considered in patients who are taking cationic medications.

DPP-4 inhibitor use with an insulin secretagogue, such as a sulfonylurea, or insulin may increase the incidence of hypoglycemia. A reduced dose of the insulin secretagogue or insulin may be needed.

Alcohol may potentiate the effect of metformin on lactate metabolism. Advise patients prescribed a metformin-containing agent against excessive alcohol consumption.

SGLT2 inhibitors (component of Glyxambi, Trijardy XR, Qtern, Qternmet XR, and Steglujan) increase urinary glucose excretion and will lead to positive urine glucose tests. In addition, 1,5-anhydroglucitol (1,5-AG) assessments are unknot reliable for evaluating glycemic control in patients taking SGLT2 inhibitors.

GLP-1 Receptor Agonists

GLP-1 inhibitors may also affect gastric emptying time and may reduce the extent and rate of absorption of orally-administered drugs that are given concomitantly. Patients should take oral medications at least 1 hour before exenatide, lixisenatide, and lixisenatide/insulin glargine injections. In clinical trials, dulaglutide, liraglutide, and injectable semaglutide did not affect the absorption of tested orally-administered medications to any clinically relevant degree; however, caution should be exercised when oral medications are given concomitantly with liraglutide. Oral contraceptives should be taken at least 1 hour before lixisenatide/insulin glargine administration or 11 hours after the dose.

Oral semaglutide (Rybelsus) should be taken at least 30 minutes prior to other orally administered medications because it can delay gastric emptying and may affect absorption of the other oral medications.

When used in combination with metformin, no increase in the incidence of hypoglycemia was observed with GLP-1 agonists compared to placebo. However, GLP-1 agonist use with an insulin secretagogue, such as a sulfonylurea, or insulin may increase the incidence of hypoglycemia. A reduced dose of the insulin secretagogue or insulin may be needed.

There are post-marketing reports of increased international normalized ratio (INR), sometimes associated with bleeding, with concomitant use of warfarin and exenatide (Byetta); however, exenatide was not shown to have a significant effect on INR in a clinical study. Exenatide ER (Bydureon, Bydureon Bcise) has not been studied with warfarin. Prothrombin time should be monitored more closely after initiation or change in all formulations of exenatide (Byetta, Bydureon, Bydureon BCISE) therapy in patients also on warfarin.

Administration of exenatide (Byetta, Bydureon, Bydureon Bcise) decreased exposure of lovastatin by 40% and delayed the time to maximum serum concentration (Tmax) and decreased maximum serum concentration (Cmax) of lovastatin. However, in a 30-week clinical trial, concurrent use of the medications was not associated with consistent changes in lipid profiles.

ADVERSE EFFECTS[159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186]

Drug	Nausea	Vomiting	Diarrhea	Headache	Hypoglycemia	URI
Amylin Analogue						
pramlintide (Symlin)	28-48 (12-17)	8-11 (4-7)	nr	5-13 (7)	4.7-16.8 (2.1-10.8)	nr
DPP-4 Inhibitors						
alogliptin (Nesina)	nr	nr	nr	4.2 (2.5)	1.5 (1.6)	4.2 (2.1)
alogliptin/metformin (Kazano)	25.5 (8.3) (metformin monotherapy)	25.5 (8.3) (metformin monotherapy)	5.5 (2.8)	5.3 (2.8)	1.9 (1.8)	8.0 (2.8)
alogliptin/ pioglitazone (Oseni)	nr	nr	nr	reported	0.8-3.8 (0.8)	4.1 (3.3)
linagliptin (Tradjenta)	nr	nr	3.3 (3)	reported	7.6 (4.1)	2.4 (1.1)
linagliptin/empagliflozin (Glyxambi)	1.1-2.3 (empagliflozin monotherapy)	nr	3-3.3 (linagliptin monotherapy)	nr	2.2-3.6	7
linagliptin/empagliflozin/ metformin ER (Trijardy XR)	reported	reported	2.2-6.6	5.1	0.7	8-10.3
linagliptin/metformin (Jentadueto, Jentadueto XR)	reported	reported	6.3	nr	reported	nr
saxagliptin (Onglyza)	nr	2.2-2.3 (1.3)	nr	6.5 (5.9)	4.0-5.6 (4.1)	7.7 (7.6)
saxagliptin/dapagliflozin (Qtern)	nr	nr	3.7	4.3	1.6	5.7
saxagliptin/dapagliflozin/ metformin ER (Qternmet XR)	nr	nr	3.7	4.3	1	13.6
saxagliptin/ metformin ER (Kombiglyze XR)	nr	nr	6.9 (11.2)	7.5 (5.2)	3.4-7.8 (5)	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported.

Adverse Effects (continued)

Drug	Nausea	Vomiting	Diarrhea	Headache	Hypoglycemia	URI
DPP-4 Inhibitors *(continued)*						
sitagliptin (Januvia)	1.4 (0.6)	nr	3 (2.3)	1.1-5.9 (2.8-4.6)	0.6-15.5 (0.6-1.8)	4.5-6.3 (3.4-5.1)
sitagliptin/ertugliflozin (Steglujan)*	nr	nr	nr	2.9-3.5 (2.3)	3.1-6.1 (1)	4-4.1 (3.9)
sitagliptin/metformin (Janumet, Janumet XR)	4.8 (1.1)	2.2 (0.6)	7.5 (4.0)	5.9 (2.8)	15.3-16.4 (0.9-8.2)	6.2 (5.1)
GLP-1 Receptor Agonists						
dulaglutide (Trulicity)	12.4-21.1 (5.3)	6-12.7 (2.3)	8.9-12.6 (6.7)	nr	0.3-0.7	nr
exenatide (Byetta)	8-44 (0-18)	4-13 (0-4)	≥1-13 (0-6)	9 (6)	3.8-35.7 (3.3-12.6)	nr
exenatide ER (Bydureon)	11.3-27	10.8-11.3	9.3-20	6.1-9.9	0-20	nr
exenatide ER (Bydureon Bcise)	8.2	3.4	4	4.4	0-25 (severe)	nr
liraglutide (Victoza)	18-20 (5)	6-9 (2)	10-12 (4)	10-11 (7)	21.2	6-7 (6)
liraglutide/insulin degludec (Xultophy)	7.8	reported	7.5	9.1	reported	5.7
lixisenatide (Adlyxin)	25 (6)	10 (2)	8 (6)	9 (6)	2 (2)	nr
lixisenatide/insulin glargine (Soliqua)	10	nr	7	5.4	8.1-17.8	5.5
semaglutide (Ozempic)	15.8-20.3 (6.1)	5-9.2 (2.3)	8.5-8.8 (1.9)	nr	1.6-3.8 (0)	nr
semaglutide (Rybelsus)	11-20 (6)	6-8 (3)	9-10 (4)	nr	6	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported.

*Values reported for sitagliptin/ertugliflozin (Steglujan) were based on data from clinical studies of ertugliflozin as add-on to sitagliptin, with or without metformin.

Nausea due to pramlintide (Symlin) may decrease over time.

Peripheral edema was reported more commonly in patients treated with combination of alogliptin or saxagliptin and a thiazolidinedione.

Other common adverse reactions reported more often with dulaglutide (Trulicity) compared to placebo are abdominal pain (6.5% to 9.4%) and decreased appetite (4.9% to 8.6%).

Other common adverse effects with exenatide ER (Bydureon) included gastroesophageal reflux (7.4%), constipation (6.3% to 10.1%), dyspepsia (5% to7.3%), decreased appetite (5%), and fatigue (5.6% to 6.1%). Injection site nodule (10.5%), injection site pruritus (3.2%), dizziness (2.5%), injection site erythema (2.3%), and constipation (2.1%) were reported with exenatide ER (Bydureon Bcise). Dyspepsia and gastroesophageal reflux were also reported with exenatide (Byetta) use (6% and 3%, respectively).

In 5 comparator-controlled 24 to 30 week trials, injection site reactions were observed more frequently in patients treated with exenatide ER (Bydureon; 17.1%) than in patients treated with exenatide (Byetta; 12.7%). One percent of patients treated with exenatide ER (Bydureon) withdrew due to injection site adverse reactions (injection site mass, injection site nodule, injection site pruritus, and injection site reaction). Cases of serious injection-site reactions, including abscess, cellulitis, and necrosis, have been reported post-marketing with exenatide ER (Bydureon) use.

In clinical trials with exenatide ER (Bydureon Bcise), frequent adverse reactions leading to discontinuation of therapy were diarrhea (0.7%), nausea (0.7%), vomiting (0.5%) and injection-site nodule (0.5%).

In pediatrics, overall, the type and severity of adverse reaction associated with liraglutide were similar to that reported in adults.

In the LEADER trial, acute event of gallbladder disease (cholelithiasis, cholecystitis) was reported more often with liraglutide (Victoza) than with placebo (3.1% versus 1.9%, respectively). Most events required hospitalization or cholecystectomy. In addition, elevated serum lipase of 3 times the upper limit of normal (ULN) occurred in 7.9% of patients treated with liraglutide versus 4.5% treated with placebo.

In a clinical trial with linagliptin (Tradjenta) patients with T2DM and micro- or macroalbuminuria, a 30% mean increase in lipase concentrations from baseline to 24 weeks was reported compared to a 2% mean decrease with placebo. Lipase levels greater than 3 x ULN were observed at rate of 8.2% and 1.7% for linagliptin and placebo, respectively.

Other common adverse reactions reported more often with injectable semaglutide (Ozempic) compared to placebo are abdominal pain (5.7% to 7.3%) and constipation (3.1% to 5%).

Other common adverse reactions reported more often with oral semaglutide (Rybelsus) compared to placebo are abdominal pain (10% to 11% versus 4%, respectively), decreased appetite (6% to 9% versus 1%, respectively), and constipation (5% to 6% versus 2%, respectively).

Other common adverse reactions reported with linagliptin/empagliflozin (Glyxambi) include urinary tract infections (11.4% to 12.5%) and nasopharyngitis (5.9% to 6.6%).

Other common adverse effects reported with sitagliptin/ertugliflozin (Steglujan) include (Steglujan versus placebo) vaginal pruritus (2.4% to 2.8% versus 0.4%, respectively), increased urination (2.4% to 2.7% versus 1%, respectively), weight decrease (1.2% to 2.4% versus 1%, respectively), and thirst (1.4% to 2.4% versus 0.6%, respectively).

Common adverse effects reported with saxagliptin/dapagliflozin (Qtern) include upper respiratory tract infection (13.6%), dyslipidemia (5.1%), back pain (3.3%), genital infection (3%), and arthralgia (2.4%). No reported episodes of major hypoglycemia occurred in clinical trials.

Risk of hypoglycemia increases in patients treated when a DPP-4 inhibitor or GLP-1 agonist are used in combination with a sulfonylurea or insulin.

Documented severe or confirmed symptomatic hypoglycemia (blood glucose ≤ 56 mg/dL) occurred in 8.3% to 10.7% of patients treated with injectable semaglutide as add-on therapy to basal insulin, with or without metformin (versus 5.3% treated with placebo).

In clinical trials, at 26 weeks, severe hypoglycemia requiring assistance was reported in 1% patients treated with oral semaglutide 7 mg monotherapy versus no cases reported in patients who received semaglutide 14 mg or placebo. Also at 26 weeks, documented severe symptomatic hypoglycemia (plasma glucose < 54 mg/dL) occurred in 0 patients treated with oral semaglutide as monotherapy (versus 1% treated with placebo). At 52 weeks, 26% to 30% of patients treated with oral semaglutide as add-on therapy to insulin, with or without metformin, reported severe symptomatic hypoglycemia (versus 32% treated with placebo).

In 2 clinical trials with lixisenatide/insulin glargine (Soliqua), severe symptomatic hypoglycemia that required medical assistance was reported in up to 1.1% of patients and symptomatic cases with self-monitoring occurred in approximately 25% and 40% of patients. In clinical trials, severe hypoglycemia was reported in zero to 0.5% of patients treated with liraglutide/insulin degludec (Xultophy).

In dulaglutide clinical trials, incidence of drug-neutralizing antibodies was 0.9%. Clinical significance of ADAs to liraglutide or semaglutide efficacy is unknown. Labeling for exenatide and lixisenatide advises to consider an alternative antidiabetic agent if desired response is not achieved. In pediatric patients (ages 10 to 17 years) treated with liraglutide, ADAs occurred in 1.5% of patients; however, no neutralizing antibodies were detected.

SPECIAL POPULATIONS[187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204,205,206,207,208,209,210,211,212]

Pediatrics

Safety and efficacy of liraglutide have been established in patients age ≥ 10 year with T2DM. Safety and efficacy have not been established for use of the remaining agents in this review in pediatric populations.

Pregnancy

Liraglutide (Victoza) is Pregnancy Category C. Previously Pregnancy Category C, the labeling for pramlintide (Symlin) has been updated to comply with the Pregnancy and Lactation Labeling Rule (PLLR) and advises that data in pregnant women are not sufficient to inform of adverse maternal or fetal outcomes.

The combination products linagliptin/empagliflozin (Glyxambi), linagliptin/empagliflozin/metformin ER (Trijardy XR), saxagliptin/dapagliflozin (Qtern), saxagliptin/dapagliflozin/metformin ER (Qternmet XR), and sitagliptin/ertugliflozin (Steglujan) are not recommended during the second and third trimesters of pregnancy, based on data in animals showing adverse renal effects from the SGLT2 inhibitor component.

Labeling for the DPP-4 inhibitor products alogliptin (Nesina), alogliptin/metformin (Kazano), alogliptin/pioglitazone (Oseni), linagliptin (Tradjenta), linagliptin/metformin (Jentadueto), linagliptin/metformin ER (Jentadueto XR), saxagliptin (Onglyza), and saxagliptin/metformin ER (Kombiglyze XR), sitagliptin (Januvia), sitagliptin/metformin (Janumet), sitagliptin/metformin ER (Janumet XR), and the GLP-1 agonist products dulaglutide (Trulicity), exenatide (Byetta, Bydureon, Bydureon BCise), lixisenatide (Adlyxin), lixisenatide/insulin glargine (Soliqua), liraglutide/insulin degludec (Xultophy), and semaglutide (Ozempic, Rybelsus) comply with the current Pregnancy and Lactation Labeling Rule and advise that there are insufficient data to determine a drug-associated risk for major birth defects or miscarriage; however, poorly controlled diabetes present risks to the mother and fetus.

A pregnancy registry exists to monitor pregnancy outcomes in women exposed to sitagliptin-containing products during pregnancy.

The potential exists for unintended pregnancy in premenopausal women treated with metformin, as it may result in ovulation in some anovulatory women.

Geriatric

The drug label for linagliptin/metformin (Jentadueto) advises against its use in patients ≥ 80 years old, unless normal renal function has been documented.

Due to the SGLT2 inhibitor component, linagliptin/empagliflozin (Glyxambi) could affect the hydration status in patients ≥ 75 years of age and could have decreased efficacy in those with renal impairment in this age group. Labeling for saxagliptin/dapagliflozin (Qtern) and sitagliptin/ertugliflozin (Steglujan) advises that these agents should be used with caution in elderly patients due to potential for decreased renal function.

Sitagliptin is substantially excreted by the kidney; renal function should be assessed more frequently in elderly patients taking sitagliptin.

No overall differences in safety or efficacy of the remaining products in this class were observed between patients ≥ 65 years and younger patients; however, since elderly patients are more likely to have decreased renal function, use of these agents in this population should be considered carefully, particularly with agents that also contain metformin which is substantially excreted by the kidney.

Renal Impairment

Metformin-containing dual combination products (Janumet, Janumet XR, Jentadueto, Jentadueto XR, Kazano, Kombiglyze XR) in this review are contraindicated in patients with an eGFR < 30 mL/min/1.73m^2. Alogliptin/metformin (Kazano), is not recommended in those with eGFR 30 to 60 mL/min/1.73m^2; the remainder of the metformin-containing products are not recommended with eGFR 30 to 45 mL/min/1.73m^2 and, if eGFR falls below 45 mL/min/1.73m^2 during therapy with these products, benefits and risks of continued therapy should be assessed.

Use pramlintide, dulaglutide, liraglutide, and lixisenatide with caution in patients with renal impairment; no dosage adjustment is needed.

Exenatide (Byetta and Bydureon BCise) is not recommended for use in patients with severe renal impairment (creatinine clearance [CrCl] < 30 mL/min, eGFR < 30 mL/min/1.73 m^2) or ESRD and should

be used with caution in renal transplant recipients. Labeling for exenatide ER (Bydureon) has been updated to advise that an increased exposure to exenatide has been found in patients with mild or moderate renal impairment and may lead to nausea and vomiting with transient hypovolemia and may worsen renal function. Exenatide is not recommended in patients with eGFR < 45 mL/min/1.73 m^2 or ESRD.

Liraglutide/insulin degludec (Xultophy) has not been studied in patients with severe renal impairment. Lixisenatide (Adlyxin) has not been studied in patients with ESRD and is, therefore, not recommended in this population. Patients with renal impairment may require more frequent glucose monitoring as this population may have increase circulating levels of insulin. There is limited therapeutic experience in patients with end stage renal disease (eGFR < 15 mL/min/1.73 m^2) and insulin glargine/lixisenatide is not recommended for use in this population. No dosage adjustment of liraglutide (Victoza) and semaglutide (Ozempic, Rybelsus) are recommended in patients with renal impairment; however, there are limited data of their use in patients with severe impairment, including ESRD.

Linagliptin is not renally excreted; therefore, no dosage adjustment is necessary in this population.

No dose adjustment for saxagliptin (Onglyza) is necessary for patients with mild renal impairment, but patients with eGFR < 45 mL/min/1.73m^2 should receive saxagliptin 2.5 mg once daily. Saxagliptin is removed by hemodialysis. Assess renal function prior to starting saxagliptin therapy.

Linagliptin/empagliflozin (Glyxambi), linagliptin/empagliflozin/metformin ER (Trijardy XR), and sitagliptin/ertugliflozin (Steglujan) are contraindicated in patients with severe renal impairment, ESRD, or who are on dialysis. Linagliptin/empagliflozin/metformin ER (Trijardy XR) also should not be started or continued in patients with an eGFR < 45 mL/min/1.73 m^2. Safety and efficacy of ertugliflozin (a component of Steglujan) have not been established in patients with T2DM and moderate renal impairment.

Saxagliptin/dapagliflozin (Qtern) and saxagliptin/dapagliflozin/metformin ER (Qternmet XR) are contraindicated in patients with moderate to severe renal impairment (eGFR < 45 mL/min/1.73 m^2), including patients with ESRD or on dialysis. Saxagliptin/metformin ER (Kombiglyze XR) is contraindicated in patient with severe renal impairment (eGFR < 30 mL/min/1.73 m^2); limit the saxagliptin component to 2.5 mg daily for eGFR < 45 mL/min/1.73 m^2).

Renal function should be assessed prior to initiating therapy with sitagliptin and periodically during treatment. In patients with moderate renal impairment (eGFR 30 mL/min/1.73m^2 to < 45 mL/min/1.73m^2), the recommended daily dose of sitagliptin is 50 mg. In patients with severe renal impairment (eGFR < 30 mL/min/1.73m^2) or ESRD on dialysis, the recommended daily dose of sitagliptin is 25 mg.

Hepatic Impairment

Pramlintide has not been studied in patients with hepatic impairment.

No pharmacokinetic study for liraglutide/insulin degludec or lixisenatide/insulin glargine has been performed in patients with hepatic impairment. Frequent glucose monitoring and dose adjustment may be required.

No dosage adjustment of exenatide (Byetta), exenatide ER (Bydureon, Bydureon BCise), liraglutide (Victoza), lixisenatide (Adlyxin), linagliptin (Tradjenta), linagliptin/empagliflozin (Glyxambi), saxagliptin

(Onglyza), saxagliptin/dapagliflozin (Qtern), or semaglutide (Ozempic, Rybelsus) is recommended for patients with hepatic impairment. Sitagliptin/ertugliflozin is not recommended in patients with severe hepatic impairment since it has not been studied in this population; no dosage adjustment is required in those with mild or moderate impairment.

No dosage adjustment of sitagliptin is needed for patients with mild to moderate hepatic insufficiency.

Alogliptin/pioglitazone (Oseni) should be initiated with caution in patients with abnormal liver function tests.

Use of metformin-containing agents should be avoided in patients with hepatic disease.

DOSAGES[213,214,215,216,217,218,219,220,221,222,223,224,225,226,227,228,229,230,231,232,233,234,235,236,237,238,239,240]

Drug	Dosing	Time of Administration Related to Mealtime	Availability
Amylin Analogue			
pramlintide (Symlin)	T1DM: initiate at 15 mcg SC injection, titrate to 30 or 60 mcg by 15 mcg increments T2DM: initiate at 60 mcg SC injection, titrate to 120 mcg as tolerated	Prior to major meals, concurrently with insulin; decrease insulin doses 50% initially, then adjust only after reaching the target dose of pramlintide	1.5 mL, 2.7 mL pens (1 mg/mL)
DPP-4 Enzyme Inhibitors			
alogliptin (Nesina)	25 mg once daily	Take with or without food	6.25 mg, 12.5 mg, 25 mg tablets
alogliptin/metformin (Kazano)	1 tablet twice daily; adjust dose based on effectiveness and tolerability; Do not exceed 25 mg/2000 mg per day	Administer with food	12.5/500 mg,12.5/1,000 mg tablets
alogliptin/pioglitazone (Oseni)	1 tablet once daily; do not exceed 25 mg/45 mg per day	Take with or without food	12.5/15 mg, 12.5/30 mg, 12.5/45 mg, 25/15 mg, 25/30 mg, 25/45 mg tablets
linagliptin (Tradjenta)	5 mg once daily	Take with or without food	5 mg tablet
linagliptin/empagliflozin (Glyxambi)	5 mg/10 mg once daily in the morning; may increase to 5 mg/25 mg once daily	Take with or without food	5/10 mg, 5/25 mg tablets

Dosages (continued)

Drug	Dosing	Time of Administration Related to Mealtime	Availability
DPP-4 Enzyme Inhibitors *(continued)*			
linagliptin/empagliflozin/ metformin ER (Trijardy XR)	Base starting dose on patient's current regimen: ▪ In patients on metformin, with or without linagliptin, switch to Trijardy XR containing a similar total daily dose of metformin and a total daily dose of empagliflozin 10 mg and linagliptin 5 mg ▪ In patients on metformin and any regimen containing empagliflozin, with or without linagliptin, switch to Trijardy XR containing a similar total daily dose of metformin, the same total daily dose of empagliflozin and linagliptin 5 mg Take orally once daily as: ▪ Take 5/10/1,000 mg or 5/25/1,000 mg as a single tablet once daily ▪ Take 2.5/5/1,000 mg or 2.5/12.5/1,000 mg as 2 tablets together once daily	Take with a meal in the morning	2.5/5/1,000 mg, 2.5/12.5/1,000 mg, 5/10/1,000 mg, 5/25/1,000 mg tablets
linagliptin/metformin (Jentadueto)	Starting dose is 2.5 mg/500 mg twice daily for patients not already taking metformin or 2.5 mg linagliptin; may increase gradually to 2.5 mg/1,000 mg twice daily to minimize GI adverse events For patients already taking linagliptin and metformin, no dosage adjustment is needed when switching to the combination tablet	Take with meals	2.5/500 mg, 2.5/850 mg, 2.5/1,000 mg tablets

Dosages (continued)

Drug	Dosing	Time of Administration Related to Mealtime	Availability
DPP-4 Enzyme Inhibitors *(continued)*			
linagliptin/metformin ER (Jentadueto XR)	Starting dose In patients not already taking metformin: 5 mg linagliptin/1,000 mg metformin ER once daily In patients already taking metformin: 5 mg linagliptin and a similar total daily dose of metformin once daily In patients already taking linagliptin and metformin or Jentadueto: switch to Jentadueto XR containing 5 mg linagliptin and a similar total daily dose of metformin once daily Do not exceed total daily dose of linagliptin 5 mg and metformin 2,000 mg	Take with a meal	2.5/1,000 mg, 5/1,000 mg tablets
saxagliptin (Onglyza)	2.5 mg to 5 mg daily by mouth	Take with or without food	2.5 mg, 5 mg tablets
saxagliptin/dapagliflozin (Qtern)	1 tablet once daily, beginning with the 5/5 mg formulation for those not already taking dapagliflozin; otherwise, initial and subsequent dosing is based on tolerability and efficacy	Take in the morning Take with or without food Do not split, crush, or chew tablets	5/5 mg, 5/10 mg tablet
saxagliptin/dapagliflozin/ metformin ER (Qternmet XR)	Begin with the 5/5/1,000 mg or 5/5/2,000 mg for patients not already taking dapagliflozin; otherwise, initial and subsequent dosing is based on tolerability and efficacy	Take in the morning with food Swallow tablet whole; do not crush or chew Intended to be started in patients already on metformin	2.5/2.5/1,000 mg, 2.5/5/1,000 mg, 5/5/1,000 mg, and 5/10/1,000 mg tablets
saxagliptin/metformin ER (Kombiglyze XR)	1 tablet once daily; maximum per day: 5 mg saxagliptin, 2,000 mg metformin	Take with evening meal	2.5/1,000 mg, 5/500 mg, 5/1,000 mg tablets
sitagliptin (Januvia)	100 mg once daily by mouth	Take with or without food	25 mg, 50 mg, 100 mg tablets
sitagliptin/ertugliflozin (Steglujan)	Starting dose is 100/5 mg once; may increase to 100/15 mg once daily	Take in the morning Take with or without food	100/5 mg, 100/15 mg tablets
sitagliptin/metformin (Janumet)	1 tablet twice daily by mouth maximum per day: 100 mg sitagliptin, 2,000 mg metformin	Take with food Do not split, crush, or chew tablets	50/500 mg, 50/1,000 mg tablets

Dosages (continued)

Drug	Dosing	Time of Administration Related to Mealtime	Availability
DPP-4 Enzyme Inhibitors *(continued)*			
sitagliptin/metformin ER (Janumet XR)	Dosage based on patient's current sitagliptin and/or metformin regimens up to a maximum of 100 mg sitagliptin and 2,000 mg metformin daily In patients not currently on metformin: 100 mg sitagliptin and 1,000 mg metformin ER per day In patients already treated with metformin, the recommended starting dose is sitagliptin 100 mg and the previous total daily dose of metformin In patients taking metformin immediate-release 850 or 1,000 mg twice daily, the starting dose is two 50 mg sitagliptin/1,000 mg metformin ER tablets taken together once daily	Once daily with a meal preferably in the evening	50/500 mg, 50/1,000 mg, 100/1,000 mg tablets
GLP-1 Receptor Agonists			
dulaglutide (Trulicity)	0.75 mg SC once weekly; may increase to a maximum of 1.5 mg once weekly	Administer at any time of day without regard to meals	0.75 mg/0.5 mL and 1.5 mg/0.5 mL single-dose pens
exenatide (Byetta)	5 mcg SC injection twice daily; dose can be increased to 10 mcg twice daily after 1 month	Administer at any time within the 60-minute period before the morning and evening meals preferably at least 6 hours apart	1.2 mL (5 mcg/dose), 2.4 mL (10 mcg/dose) prefilled pen containing 250 mcg/mL solution
exenatide ER (Bydureon, Bydureon BCise)	2 mg SC injection administered once weekly	Administer at any time without regard to meals	Bydureon: 2 mg single-dose pen Bydureon Bcise: 2 mg auto-injector
liraglutide (Victoza)	Adults: 0.6 mg once daily SC for 1 week; increase dose to 1.2 mg once daily; may increase to 1.8 mg daily, if needed, after ≥ 1 week of 1.2 mg dose Pediatrics: 0.6 mg once daily SC for 1 week; after ≥ 1 week may increase dose to 1.2 mg once daily; may increase to 1.8 mg daily, as needed, after ≥ 1 week of 1.2 mg dosing	Administer once daily at any time of day independent of meals	Prefilled multidose pen that delivers 0.6 mg, 1.2 mg, and 1.8 mg doses; Pens contain 6 mg/mL (3 mL)

Dosages (continued)

Drug	Dosing	Time of Administration Related to Mealtime	Availability
GLP-1 Receptor Agonists *(continued)*			
liraglutide/insulin degludec (Xultophy)	In patients naïve to basal insulin or a GLP-1 agonist: initial dose is 10 units SC once daily. In patients currently on basal insulin or a GLP-1 agonist: initial dose is 16 units SC once daily; discontinue insulin or GLP-1 agonist prior to starting liraglutide/insulin degludec	Administer at the same time each day with or without food.	Prefilled multidose pen that delivers 10 to 50 units/injection Pen contains 3.6 mg/mL liraglutide and 100 units/mL insulin degludec (3 mL)
lixisenatide (Adlyxin)	10 mcg once daily SC for 14 days; on day 15 increase to 20 mcg once daily	Administer once daily within 1 hour before the first meal of the day	Starter Pak: 1 Prefilled multidose pen that deliver 14 doses of 10 mcg (50 mcg/mL) and 1 pen of 20 mcg (100 mcg/mL) per dose; Maintenance Pak: 2 prefilled multidose pens that deliver 20 mcg/dose (100 mcg/mL in 3 mL)
lixisenatide/insulin glargine (Soliqua)	In patients naïve to basal insulin or to a GLP-1 receptor agonist, currently on a GLP-1 receptor agonist, or currently on < 30 units of basal insulin daily: initial dose of lixisenatide/insulin glargine is 15 units SC once daily; discontinue basal insulin or GLP-1 agonist prior to starting lixisenatide/insulin In patients currently on 30 to 60 units of basal insulin daily, with or without a GLP-1 agonist: initial dose of lixisenatide/insulin glargine is 30 units SC once daily; discontinue basal insulin or GLP-1 agonist prior to starting lixisenatide/insulin glargine	Administer once daily within 1 hour before the first meal of the day	Prefilled, single-patient use, multidose pen that deliver 15 to 60 units per dose Pen contains lixisenatide 33 mcg and insulin glargine 100 units per mL (3 mL)
semaglutide (Ozempic)	Initial dose is 0.25 mg SC once weekly for 4 weeks; the 0.25 mg dose is not effective for glycemic control and is intended only for initiation of treatment After 4 weeks, increase to 0.5 mg once weekly; after an additional 4 weeks, may increase to 1 mg once weekly Maximum recommended dose is 1 mg once weekly	Administer on the same day each week, at any time of the day, without regard to meals If the administration day of the week is changed, at least 48 hours should be allowed between 2 doses	Prefilled multidose pens in 2 dosing increment options: one that delivers 0.25 mg or 0.5 mg per injection and another that delivers 1 mg per injection Pens contain semaglutide 2 mg/1.5 mL

Dosages (continued)

Drug	Dosing	Time of Administration Related to Mealtime	Availability
GLP-1 Receptor Agonists *(continued)*			
semaglutide (Rybelsus)	Initial dose is 3 mg orally once daily for 30 days; then increase to 7 mg once daily; if additional glycemic control is needed after 30 days of 7 mg dosing, may increase to 14 mg once daily Administration of two 7 mg tablets to achieve a 14 mg dose is not recommended Swallow tablet whole; do not crush, split, or chew	Take at least 30 minutes prior to the first food, beverage, or other oral medication of the day; waiting to eat more than 30 minutes may increase semaglutide absorption Take with ≤ 4 ounces of plain water only	3 mg, 7 mg, and 14 mg tablets

All GLP-1 agonist products should be kept refrigerated (36°F to 46°F). The manufacturers recommend that, after first use, exenatide (Byetta) can be kept at temperature not to exceed 77°F, for up to 30 days if needed; after first use, liraglutide (Victoza), and lixisenatide (Adlyxin) can be kept at room temperature, not to exceed 86°F, for up to 30 days, if needed; semaglutide may be kept at room temperature, not to exceed 86°F, for up to 56 days; liraglutide/insulin degludec (Xultophy) can be kept at room temperature, not to exceed 86°F, for up to 21 days; dulaglutide (Trulicity) and lixisenatide/insulin glargine (Soliqua) can be kept at room temperature, not to exceed 86°F, for up to 14 days. Exenatide ER (Bydureon) may be kept at room temperature not to exceed 77°F for up to 4 weeks, if needed; exenatide auto-injector (Bydureon BCise) may be kept at room temperature not to exceed 86 °F for up to 4 weeks, if needed.

Pramlintide is to be injected subcutaneously into the abdomen or thigh, rotating sites regularly.

Doses of dulaglutide (Trulicity), exenatide (Byetta, Bydureon, and Bydureon BCise), liraglutide (Victoza), lixisenatide (Adlyxin), liraglutide/insulin degludec (Xultophy), lixisenatide/insulin glargine (Soliqua), and semaglutide (Ozempic) should be injected in the thigh, abdomen, or upper arm, rotating sites regularly. Do not inject insulin-containing products into areas of lipodystrophy or localized cutaneous amyloidosis.

Patients taking oral semaglutide 14 mg daily may be switched to injectable semaglutide (Ozempic) 0.5 mg once weekly; the first SC dose may be administered the day after the last oral dose. Patients treated with SC semaglutide 0.5 mg can be switched to oral semaglutide 7 mg or 14 mg; the first oral dose may be taken up to 7 days after the last SC injection. No equivalent dose of oral semaglutide exists that compares to the SC semaglutide 1 mg dose.

Patients with moderate to severe renal impairment (CrCl ≤ 50 mL/min), ESRD, and taking strong CYP3A4/5 inhibitors (ketoconazole, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin) should receive no more than saxagliptin 2.5 mg once daily.[241]

Patients with eGFR < 45 mL/min/1.73m^2 should receive saxagliptin 2.5 mg once daily.

In patients with moderate renal impairment (eGFR ≥ 30 mL/min/1.73 m^2 to < 45 mL/min/1.73 m^2), the recommended daily dose of sitagliptin is 50 mg. In patients with severe renal impairment (eGFR < 30 mg/min/1.73m^2) or ESRD on dialysis, the recommended daily dose of sitagliptin is 25 mg.

Adjust pramlintide (Symlin) doses when there has been no clinically significant nausea for at least 3 days. When switching patients from pramlintide vial to pens, convert doses from units to micrograms (mcg): 2.5 units=15 mcg, 5 units=30 mcg, 10 units=60 mcg, and 20 units=120 mcg.

Initiating exenatide (Byetta) therapy at 5 mcg dosage, liraglutide at 0.6 mg, and lixisenatide at 10 mcg, reduces the incidence and severity of gastrointestinal side effects.

Gradually increase the dose of metformin-containing products to reduce the gastrointestinal side effects of metformin.

Prior treatment with exenatide (Byetta) is not required when initiating exenatide ER (Bydureon, Bydureon BCise) therapy. Patients changing from exenatide (Byetta) to exenatide ER (Bydureon, Bydureon BCise) may experience transient (approximately 2 weeks) elevations in blood glucose concentrations.

Alogliptin/metformin, alogliptin/pioglitazone, linagliptin/metformin ER (Jentadueto XR), linagliptin/empagliflozin/metformin ER (Trijardy XR), saxagliptin/metformin ER (Kombiglyze XR), sitagliptin/metformin ER, saxagliptin/dapagliflozin (Qtern), and saxagliptin/dapagliflozin/metformin ER (Qternmet XR) tablets should be swallowed whole and never crushed, cut, or chewed. The inactive ingredients of saxagliptin/dapagliflozin (Qtern) may be excreted as a soft mass in the feces that resemble the original tablet.

Patients who require < 15 units or > 60 units of lixisenatide/insulin glargine (Soliqua) should be prescribed an alternative antidiabetic agent. Do not split the dose or mix either product with other insulins. If a dose of either agent is missed, therapy should be resumed with the next scheduled dose at the prescribed dosage.

When an iodinated contrast imaging, including intra-arterial, procedure is required, discontinue metformin-containing products (Kazano, Janumet, Janumet XR, Jentadueto, Jentadueto XR, Kombiglyze XR, Trijardy XR) at the time of, or prior to the procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m^2; or in patients with a history of liver disease, alcoholism, or heart failure. Reassess eGFR 48 hours after the procedure; in general, restart the medication if renal function is stable. Labeling for saxagliptin/dapagliflozin/metformin ER (Qternmet XR) contains similar instructs to hold dosing around iodinated contrast agent administration in patients with a history of liver disease, alcoholism, or heart failure, but does not restrict based on eGFR; however, the product is contraindicated in patients with eGFR < 45 mL/min/1.73 m^2.

The initial dose of pioglitazone, in alogliptin/pioglitazone (Oseni), should not exceed 15 mg once daily in patients with NYHA Class I or II heart failure. The dosage of pioglitazone should not exceed 15 mg daily in patients also taking strong CYP2C8 inhibitors. In patients with moderate renal impairment (CrCl ≥ 30 to < 60 mL/min) recommended dosage of alogliptin component is 12.5 mg daily in alogliptin-containing products (Nesina, Oseni).

The liraglutide/insulin degludec (Xultophy) pen dials the dose in 1 unit increment and caution should be used in patients with visual impairment who may rely on audible clicks to dial the dose.

CLINICAL TRIALS

Search Strategies

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

The method of administration and associated monitoring makes it difficult to perform properly blinded studies with injectable drugs. Due to the low number of double-blind studies, open-label studies have been included. While the large studies may produce accurate results, study design should be taken into consideration.

Since 2008, the FDA requires pre-marketing studies that assess the cardiovascular (CV) risk of new antidiabetic agents.[242] Study criteria consist of (1) an upper bound of 95% confidence interval of < 1.3 for the risk ratio of important CV events; (2) inclusion of patients with relatively advanced disease, elderly, and those with renal impairment; (3) a minimum of 2 years safety data; (4) prospective data with independent adjudication of CV events in all phase 2 and 3 studies; and (5) a meta-analyses of CV events may also be included. In addition, in a draft guidance, the FDA suggests long-term post-approval CV studies be conducted to assess the effect on CV outcomes with antidiabetic agents.[243] CV outcomes studied will be included in this review when available.

Amylin Analogues

pramlintide (Symlin) versus placebo

In a double-blind, placebo-controlled, parallel-group, multicenter study, 651 patients with T1DM were randomized to mealtime injections of placebo or pramlintide in addition to insulin therapy for 52 weeks.[244] Addition of pramlintide 60 mcg 3 or 4 times daily to insulin resulted in significant reductions in HbA1c from baseline of 0.29% ($p<0.011$) and 0.34% ($p<0.001$), respectively, compared to a 0.04% reduction in the placebo group at 52 weeks. Greater reduction in HbA1c with pramlintide was achieved without an increase in concomitant insulin use and was accompanied by a significant reduction in body weight from baseline to week 52 of -0.4 kg in the pramlintide 60 mcg three ($p<0.027$) or four times daily ($p<0.04$) groups The placebo group had a +0.8 kg weight gain. The most frequent adverse event in pramlintide-treated patients was nausea.

A 29-week, double-blind, placebo-controlled study randomized 296 patients with T1DM to pramlintide or placebo as an adjunct to insulin.[245] Insulin use was adjusted as needed. Baseline HbA1c was 8.1% for both groups. At week 29, HbA1c reductions were similar for both study arms (both -0.5%). Pramlintide

treatment significantly reduced postprandial glucose excursions (p<0.0005) and weight (pramlintide -1.3 ± 0.3 kg; placebo +1.2 ± 0.3 kg; p<0.0001). At week 29, insulin dose decreased by 28% and 4% in pramlintide- and placebo-treated groups, respectively. Nausea was reported by 63% and 36% of patients in pramlintide and placebo groups (p<0.01), respectively, and severe hypoglycemia rates were 0.57 for pramlintide and 0.30 for placebo (event rate/patient-year; p<0.05).

In a 52-week, double-blind, placebo-controlled, parallel-group, multicenter study, 656 patients with T2DM treated with insulin alone or in combination with sulfonylureas and/or metformin were randomized to receive additional preprandial injections of either placebo or pramlintide.[246] Pramlintide doses were 60 mcg three times a day, 90 mcg twice daily, or 120 mcg twice daily. Treatment with pramlintide 120 mcg twice daily resulted in sustained reduction in HbA1c from baseline (-0.68% and -0.62% at weeks 26 and 52, respectively), compared to placebo (p<0.05). The percentage of patients achieving HbA1c < 8% was 46% for the pramlintide group and 28% for the placebo group (p<0.05). Glycemic improvement with pramlintide 120 mcg twice daily was accompanied by a mean weight loss of 1.4 kg compared to weight gain of +0.7 kg with placebo at week 52 (p<0.05). The most common adverse event associated with pramlintide use was transient, mild to moderate nausea.

DPP-4 Inhibitors

alogliptin (Nesina) versus pioglitazone and alogliptin/pioglitazone (Oseni)

A total of 655 patients with a mean baseline HbA1c of 8.8% were randomized to receive alogliptin 25 mg alone, pioglitazone 30 mg alone, alogliptin 12.5 mg with pioglitazone 30 mg, or alogliptin 25 mg with pioglitazone 30 mg once daily in a double-blind, active-controlled study over 26 weeks.[247,248] Mean baseline HbA1c and fasting plasma glucose (FPG) were similar between the groups. Both combination therapy groups had statistically significant improvements from baseline HbA1c and FPG compared to alogliptin 25 mg alone and pioglitazone 30 mg alone (95% CI, p<0.01). The percentage of patients achieving an HbA1c ≤ 7% was 24%, 34%, 53% and 63% for patients taking alogliptin 25 mg alone, pioglitazone 30 mg alone, alogliptin 12.5 mg with pioglitazone 30 mg, and alogliptin 25 mg with pioglitazone 30 mg, respectively (p<0.01). The mean decrease in baseline FPG was 26 mg/dL, 37 mg/dL, 49 mg/dL, and 50 mg/dL for alogliptin 25 mg alone, pioglitazone 30 mg alone, alogliptin 12.5 mg with pioglitazone 30 mg, and alogliptin 25 mg with pioglitazone 30 mg, respectively.

alogliptin (Nesina) versus metformin versus alogliptin/metformin (Kazano)

A total of 784 patients with a mean baseline HbA1c of 8.4% were randomized to 1 of 7 treatment groups (placebo, metformin 500 mg or 1,000 mg twice daily, alogliptin 12.5 mg or 25 mg twice daily, or alogliptin 12.5 mg with metformin 500 mg or 1,000 mg twice daily) in a double-blind, placebo-controlled study for 26 weeks.[249] Patients treated with the combination regimens had statistically significant improvements in HbA1c and FPG compared to patients treated with alogliptin or metformin alone (95% CI, p<0.05). The percentage of patients achieving an HbA1c < 7% was 4%, 20%, 27%, 34%, 47%, and 59% for patients taking placebo, alogliptin 12.5 mg alone, metformin 500 mg alone, metformin 1,000 mg alone, alogliptin 12.5 mg plus metformin 500 mg, and alogliptin 12.5 mg plus metformin 1,000 mg, respectively (p<0.05). The FPG change from baseline was +12 mg/dL, -10 mg/dL, -12 mg/dL, -32 mg/dL, -32 mg/dL, and -46 mg/dL, respectively.

alogliptin/metformin (Kazano) versus metformin

In a placebo-controlled study, 527 patients with T2DM already on metformin at doses of at least 1,500 mg per day or at maximum tolerated dose were randomized to receive alogliptin 12.5 mg or 25 mg, or placebo and were maintained on a stable dose of metformin (mean dose equal to 1,700 mg) during a 26 week study.[250] Patients who were treated with alogliptin 25 mg plus metformin had statistically significant improvements in HbA1c and FPG compared to patients receiving placebo (95% CI, p<0.001). Patients had a mean baseline HbA1c of 7.9% and 8% for the alogliptin 25 mg plus metformin group and placebo plus metformin group, respectively. The percent of patients achieving an HbA1c of less than or equal to 7% was 44% and 18% for the alogliptin 25 mg with metformin group and placebo with metformin group, respectively (p<0.001). The FPG change from baseline was -17 mg/dL and zero mg/dL for patients treated with alogliptin 25 mg with metformin and patients treated with placebo with metformin, respectively.

alogliptin (Nesina) plus metformin versus alogliptin/metformin (Kazano) plus pioglitazone versus metformin plus placebo versus metformin plus pioglitazone

In a double-blind, placebo-controlled study, 1,554 patients with T2DM already on metformin at doses of at least 1,500 mg per day or at maximum tolerated dose were randomized to 1 of 12 treatment groups (placebo, 12.5 mg or 25 mg of alogliptin alone, 15 mg, 30 mg, or 45 mg of pioglitazone alone, or 12.5 mg or 25 mg of alogliptin with 15 mg, 30 mg, or 45 mg of pioglitazone) and maintained on a stable dose of metformin (mean dose equal to 1,700 mg) during a 26-week study.[251] Patients treated with alogliptin with pioglitazone had statistically significant improvements in HbA1c and FPG compared to patients treated with placebo, alogliptin alone, or pioglitazone alone when added to background metformin treatment (95% CI, p≤0.01). The percentage of patients achieving an HbA1c ≤ 7% was 6%, 27%, 26%, 30%, 36%, 55%, 53%, and 60% in patients treated with placebo, alogliptin 25 mg, pioglitazone 15 mg, 30 mg, and 45 mg, alogliptin 25 mg with pioglitazone 15 mg, alogliptin 25 mg with pioglitazone 30 mg, and alogliptin 25 mg with pioglitazone 45 mg, respectively (p≤0.01). The mean change from baseline in FPG was 7 mg/dL, -19 mg/dL, -24 mg/dL, -29 mg/dL, -32 mg/dL, -38 mg/dL, -42 mg/dL, -53 mg/dL in patients treated with placebo, alogliptin 25 mg, pioglitazone 15 mg, 30 mg, and 45 mg, alogliptin 25 mg with pioglitazone 15 mg, alogliptin 25 mg with pioglitazone 30 mg, and alogliptin 25 mg with pioglitazone 45 mg, respectively.

alogliptin plus pioglitazone/metformin versus pioglitazone/metformin

In an active-comparator study over 52 weeks, 803 patients with T2DM who were insufficiently controlled on their current pioglitazone 30 mg and metformin (daily dose of at least 1,500 mg or at maximum tolerated dose) therapy were randomized to receive the addition of alogliptin 25 mg or to titrate their pioglitazone dose from 30 mg to 45 mg.[252] Patients were maintained on a stable dose of metformin (median dose equal to 1,700 mg). Prior to randomization, patients underwent a 4-week single-blind, placebo run-in period. Patients treated with the addition of alogliptin 25 mg with pioglitazone and metformin had statistically significant improvements in their HbA1c and FPG (p<0.001) compared to patients who had their pioglitazone dose increased from 30 mg to 45 mg (95% CI). The percent of patients achieving an HbA1c of less than 7% was 33% (alogliptin 25 mg with pioglitazone 30 mg and metformin) and 21% (pioglitazone 45 mg with metformin) (p<0.001). The mean change from baseline in FPG was -15 mg/dL (alogliptin 25 mg with pioglitazone 30 mg and metformin) and negative 4 mg/dL (pioglitazone 45 mg with metformin).

alogliptin/pioglitazone (Oseni) versus pioglitazone with or without sulfonylurea or metformin

A 26-week, placebo-controlled study was performed in 493 patients with T2DM who were insufficiently controlled on a thiazolidinedione alone or in combination with a sulfonylurea or metformin.[253] Prior to randomization, patients underwent a 4-week single-blind, placebo run-in period. Patients had a mean baseline HbA1c of 8% and were randomized to receive alogliptin 12.5 mg or 25 mg, or placebo. During the treatment period, patients were maintained on a stable dose of pioglitazone (median dose of 30 mg). Patients who were previously treated with metformin (median dose equals 2,000 mg) or sulfonylurea (median dose of 10 mg) were maintained on therapy throughout the treatment period. Statistically significant improvements in baseline HbA1c and FPG occurred in patients who had alogliptin 25 mg daily added to their pioglitazone therapy compared to placebo (95% CI, p<0.01). The percentage of patients achieving an HbA1c ≤ 7% was 49% (alogliptin 25 mg with pioglitazone with or without metformin or a sulfonylurea) and 34% (placebo with pioglitazone with or without metformin or a sulfonylurea) (p<0.01). The mean change from baseline for FPG was -20 mg/dL (alogliptin 25 mg with pioglitazone with or without metformin or a sulfonylurea) and -6 mg/dL (placebo with pioglitazone with or without metformin or a sulfonylurea).

alogliptin (Nesina) and cardiovascular outcomes

In the EXAMINE study, 5,380 patients with diabetes and an acute MI/unstable angina requiring hospitalization were randomized to alogliptin or placebo in addition to existing antihyperglycemic and CV drug therapy.[254] The primary endpoint, a composite of CV death, nonfatal MI, and nonfatal stroke, occurred at similar rates for alogliptin and placebo (hazard ratio [HR], 0.96; 95% CI 0.8 to 1.16). HbA1c levels were significantly reduced with alogliptin, a mean difference of -0.36%. No increase in hypoglycemia or any increased risks of cancer or pancreatitis were observed.

linagliptin (Tradjenta)

In 2 double-blind, multicenter trials (n>350 evaluable patients/trial) in adult patients with inadequately controlled T2DM, oral linagliptin monotherapy was significantly more effective than placebo in improving glycemic control with placebo-corrected adjusted mean changes in HbA1c levels of -0.69% to -0.88% after 12 or 24 weeks. Linagliptin was generally well tolerated in clinical trials, having neutral or minimal effects on bodyweight and generally being associated with a very low incidence of hypoglycemia.[255]

A multi-center, 24-week randomized, double-blind, parallel group study in 1,058 patients comparing linagliptin and placebo when added to metformin plus sulfonylurea in persons with T2DM inadequately controlled (HbA1c of 7% to 10%) by metformin plus sulfonylurea. [256] At week 24, the linagliptin placebo-corrected HbA1c adjusted mean change from baseline was -0.62% (p<0.0001). Fasting plasma glucose was reduced with linagliptin relative to placebo (-0.7 mmol/L, 95% CI -1 to -0.4; p<0.0001). Symptomatic hypoglycemia occurred in 16.7% and 10.3% of the linagliptin and placebo groups, respectively. Hypoglycemia was generally mild or moderate; severe hypoglycemia was reported in 2.7% and 4.8% of the participants experiencing hypoglycemic episodes in the linagliptin and placebo arms, respectively. No significant weight changes were noted.

In a 24-week study, patients with T2DM were randomized to receive the initial combination of 30 mg pioglitazone plus 5 mg linagliptin (n=259) or pioglitazone plus placebo (n=130).[257] The primary endpoint of change from baseline in HbA1c with the initial combination of linagliptin plus pioglitazone

was -1.06% compared with -0.56% for placebo plus pioglitazone (95% CI -0.71, -0.3; p<0.0001). Reductions in FPG were significantly greater for linagliptin plus pioglitazone than with placebo plus pioglitazone; -1.8 and -1 mmol/L, respectively, (95% CI -1.2, -0.4; p<0.0001). Patients taking linagliptin plus pioglitazone, compared with those receiving placebo plus pioglitazone, were more likely to achieve HbA1c < 7% (42.9% versus 30.5%, respectively; p=0.0051) and reduction in HbA1c of at least 0.5% (75% versus 50.8%, respectively; p<0.0001). Hypoglycemic episodes, all mild in severity, occurred in 1.2% of the linagliptin plus pioglitazone patients and none in the placebo plus pioglitazone group.

In a double-blind, placebo-controlled trial, patients with inadequately controlled T2DM on sulfonylurea monotherapy were randomly assigned to receive treatment with linagliptin 5 mg once daily or placebo as adjunctive therapy to sulfonylurea therapy.[258] Mean baseline characteristics were similar in the linagliptin and placebo groups. Linagliptin treatment was associated with a placebo-corrected mean (95% CI) change in HbA1c from baseline to 18 weeks of -0.47% (p<0.0001). Patients in the linagliptin group were more likely to achieve the HbA1c target level of <7% after 18 weeks of treatment (15.2% versus 3.7%, respectively; odds ratio [OR] = 6.5; 95% CI, 1.7-24.8; p=0.007). The overall frequency of adverse events was similar between the linagliptin and placebo groups, including incidences of hypoglycemia, and none of the hypoglycemic episodes were assessed as severe by the investigator. Changes in mean body weight was similar in both groups (p=0.12).

linagliptin (Tradjenta) and cardiovascular outcomes and renal events

The CARMELINA trial randomized patients with T2DM and at high risk of CV and renal events to linagliptin 5 mg once daily (n=3,494) or placebo (n=3,485) added to usual care.[259] Patients had a baseline HbA1c of 6.5% to 10%. No patient had ESRD. Primary outcome was time to first occurrence of the composite of CV death, nonfatal myocardial infarction, or nonfatal stroke. After a median follow-up of 2.2 years, linagliptin met the noninferiority criteria relative to placebo, defined as a HR < 1.3 for the upper limit of the 2-sided 95% CI. The primary outcome occurred in 12.4% and 12.1%, of patients in the linagliptin and placebo groups, respectively (HR, 1.02; 95% CI, 0.89 to 1.17; p<0.001). Linagliptin did not meet noninferiority for the secondary outcome of first occurrence of adjudicated death due to renal failure, ESRD, or sustained 40% or higher decrease in eGFR from baseline, which occurred in 9.4% and 8.8%, of patients treated with linagliptin and placebo, respectively (HR, 1.04; 95% CI, 0.89 to 1.22; p=0.62). Adverse events occurred at similar rates between the groups (77.2% and 78.1%, respectively), including hypoglycemia (29.7% and 29.4%, respectively). Incidence of confirmed acute pancreatitis was 0.3% versus 0.1%, respectively.

The CAROLINA trial compared daily doses of linagliptin 5 mg (n=3,023) and glimepiride 1 mg to 4 mg (n=3,010) as add-on to usual care in patients with relatively early T2DM and elevated CV risk.[260] The primary outcome was time to first occurrence of CV death, nonfatal MI, or nonfatal stroke. After a median follow-up of 6.3 years, linagliptin demonstrated noninferiority to glimepiride, defined as a HR < 1.3 of the upper limit of the 2-sided 95% CI. The primary outcome occurred in 11.8% and 12% of patients in the linagliptin and glimepiride groups, respectively (HR, 0.98 [95% CI, 0.84 to 1.14]; p <0.001 for noninferiority), meeting the noninferiority criterion but not superiority (p=0.76). Adverse events occurred at similar rates between the groups. At least 1 hypoglycemic episode occurred in 10.6% of patients treated with linagliptin compared to 37.7% treated with glimepiride.

linagliptin (Tradjenta) and renal impairment

In the 24-week, double-blind, MARLINA-T2D trial, the addition of linagliptin to standard of care in patients (n=360) with T2DM (HbA1c, 6.5% to 10%), early stages of renal disease (eGFR ≥ 30 mL/min/1.73 m^2), and urinary albumin-to-creatinine ratio (UACR) 30 to 3,000 mg/g) was evaluated for impact on renal function.[261] While linagliptin significantly improved glycemic control, with a mean change in HbA1c of -0.6%, it did not significantly lower albuminuria (placebo-adjusted, time-weighted average change in UACR from baseline of -6% [95% CI, -15 to 3; p=0.195]).

linagliptin/empagliflozin (Glyxambi)

A double-blind, randomized, active-controlled study compared the safety and efficacy of linagliptin 5 mg in combination with empagliflozin 10 mg or 25 mg to the individual components in 686 patients with T2DM.[262] After a 2-week run-in period, patients who were inadequately controlled on at least 1,500 mg of metformin daily were randomized 1:1:1:1:1 to empagliflozin 10 mg, empagliflozin 25 mg, linagliptin 5 mg, linagliptin 5 mg/empagliflozin 10 mg, or linagliptin 5 mg/empagliflozin 25 mg. At week 24, the fixed dose linagliptin/empagliflozin combinations provided statistically significant improvements in HbA1c (p<0.0001) and FPG (p<0.001) compared to the individual components. The combination treatment also resulted in a statistically significant reduction in body weight compared to linagliptin (p<0.0001); however, no statistically significant differences in body weight were seen when compared to empagliflozin alone.

linagliptin/empagliflozin (Glyxambi) and cardiovascular outcomes

In the randomized, placebo-controlled EMPA-REG OUTCOME trial, empagliflozin, a component of Glyxambi, had a 14% reduction (HR, 0.86; 95% confidence interval [CI], 0.74 to 0.99; p=0.04 for superiority to placebo) in the primary composite outcome of CV death, or nonfatal myocardial infarction (MI) or stroke, when added to standard of care in 7,020 patients with T2DM.[263] A significantly lower rate of CV death (3.7% versus 5.9%), hospitalization for HF (2.7% versus 4.1%), and death from any cause (5.7% versus 8.3%) were reported with empagliflozin compared to placebo. No significant differences in the occurrence of MI or stroke were reported. CV outcomes studies have not been published for the combination product of linagliptin/empagliflozin.

The CARMELINA and CAROLINA trials evaluated CV outcomes (and renal outcomes in CARMELINA) of linagliptin, a component of Glyxambi.

linagliptin/metformin (Jentadueto)

There have been no clinical efficacy studies performed with linagliptin/metformin (Jentadueto). However, co-administration of the single entity medications has been studied in T2DM patients who were not well controlled in their diet and exercise and in combination with a sulfonylurea. The bioequivalence of linagliptin/metformin to linagliptin and metformin administered together as single entities was demonstrated in healthy subjects.

A 24-week randomized, double-blind, placebo-controlled factorial study involving 791 patients was performed to determine the efficacy of linagliptin as initial therapy with metformin.[264] Patients (52%) entering the study already on antihyperglycemic therapy went through a 4-week wash-out period followed by a 2-week placebo run-in period. Patients who had inadequate glycemic control (HbA1c ≥ 7% and ≤ 10.5%) were randomized into the study. Forty-eight percent of patients entering the study

were not taking an antihyperglycemic and went straight into the 2-week placebo run-in phase. Patients who had inadequate glycemic control (HbA1c ≥ 7.5% and < 11%) after the 2-week placebo run-in phase were randomized into the study. Randomization was stratified by baseline HbA1c (< 8.5% versus ≥ 8.5%) and prior use of an antihyperglycemic medication. Patients were randomized in a 1:2:2:2:2:2 ratio to either placebo or 1 of the 5 treatment arms (linagliptin 5 mg once daily; metformin 500 mg twice daily; linagliptin 2.5 mg twice daily plus metformin 500 mg twice daily; metformin 1000 mg twice daily; and linagliptin 2.5 mg twice daily plus metformin 1,000 mg twice daily). Initial therapy with the combination of linagliptin and metformin significantly improved HbA1c levels (change from baseline of -1.2 for linagliptin 2.5 mg/metformin 500 mg twice daily and -1.6 for linagliptin 2.5 mg/metformin 1,000 mg twice daily) compared to linagliptin monotherapy (change from baseline of -0.5), metformin monotherapy (change from baseline of -0.6 for metformin 500 mg twice daily and -1.1 for metformin 1000 mg twice daily), and placebo (change from baseline of 0.1), CI= 95%. The FPG also improved with linagliptin plus metformin (change from baseline of -33 mg/dL for linagliptin 2.5 mg/metformin 500 mg twice daily and -49 mg/dL for linagliptin 2.5 mg/metformin 1,000 mg twice daily) compared to linagliptin monotherapy (change from baseline of -9 mg/dL), metformin monotherapy (change from baseline of -16 mg/dL for metformin 500 mg twice daily and -32mg/dL for metformin 1,000 mg twice daily), and placebo (change from baseline of 10 mg/dL), CI= 95% and p<0.0001.

A 104-week double-blind, glimepiride-controlled, noninferiority study was performed in patients with T2DM with insufficient glycemic control despite being on metformin compared to patients having coadministration of linagliptin plus metformin.[265] Patients on metformin monotherapy had a run-in period of 2 weeks and patients taking metformin with another oral antihyperglycemic had a metformin monotherapy (daily dose at least 1,500 mg) run-in period of 6 weeks and washout of the other antihyperglycemic agent. After an additional 2-week placebo run-in period, patients with poor glycemic control (HbA1c 6.5% to 10%) were randomized 1:1 to the addition of linagliptin 5 mg daily (n=766) or glimepiride (n=761, initial dose 1 mg per day and titrated up to 4 mg per day as needed over 12 weeks). After 52 weeks, both groups, linagliptin plus metformin and glimepiride plus metformin, saw a decrease in HbA1c and FPG levels, -0.4% and -0.6% (CI 97.5%) and -9 mg/dL and -16 mg/dL, respectively. The incidence of hypoglycemia was lower in the linagliptin plus metformin group compared to the glimepiride plus metformin group, 5.4% and 31.8%, respectively (p< 0.0001). Patients treated with linagliptin plus metformin experienced a significant decrease from baseline body weight compared to a significant weight gain in the glimepiride plus metformin group (-1.1 kg versus +1.4 kg, p<0.0001).

A 24-week, randomized, double-blinded, placebo controlled study was performed in 1,058 patients with T2DM to assess the efficacy of linagliptin in combination with metformin and a sulfonylurea. Patients were randomized to receive linagliptin 5 mg (n=778) or placebo (n=262) once daily. Pioglitazone was used as a rescue medication for those patients having poor glycemic control. Patients treated with linagliptin plus metformin and a sulfonylurea had a reduction in HbA1c and FPG levels, -0.7% and -5 mg/dL, respectively, and patients using placebo plus metformin and a sulfonylurea had a reduction of -0.1% in HbA1c levels but an increase of 8 mg/dL in FPG levels (CI 95%). Rescue therapy was needed in 5.4% of patients treated in the linagliptin group versus 13% in the placebo group. Overall, 31.2% of the linagliptin plus metformin and sulfonylurea patients and 9.2% of the placebo plus metformin and sulfonylurea patients reached a goal of HbA1c < 7%.[266]

linagliptin/empagliflozin/metformin ER (Trijardy XR)

A phase 2 randomized, open-label trial demonstrated bioequivalence of empagliflozin, linagliptin, and metformin extended-release (ER) fixed-dose combination tablets and their individual components in healthy adults.[267] The safety profile of the fixed-dose combination was consistent with its individual components.

linagliptin/metformin ER (Jentadueto XR)

The safety and efficacy of linagliptin/metformin ER are established based on controlled studies of linagliptin and metformin co-administered separately in patients with T2DM who were inadequately controlled on diet and exercise and in combination with a sulfonylurea.[268]

saxagliptin (Onglyza)

The efficacy and safety of once-daily saxagliptin monotherapy were evaluated in treatment-naïve patients with T2DM and inadequate glycemic control for 24 weeks.[269] The study enrolled 401 patients with HbA1c of 7% to 10%. These patients were randomized and treated with oral saxagliptin 2.5 mg, 5 mg, or 10 mg once daily or placebo. Primary endpoint was HbA1c change from baseline to week 24, and secondary endpoints included change from baseline to week 24 in FPG, proportion of patients achieving HbA1c < 7%, and changes in postprandial glucose area-under-the-curve (PPG-AUC). Results demonstrated that saxagliptin significantly decreased HbA1c by -0.43%, -0.46%, -0.54% for saxagliptin 2.5 mg, 5 mg, and 10 mg, respectively, versus +0.19% for placebo (p<0.0001, all values). Adjusted mean FPG was significantly reduced from baseline (-15, -9, and -17 mg/dL) for saxagliptin 2.5 mg, 5 mg, and 10 mg, respectively, versus +6 mg/dL for placebo (p=0.0002, p=0.0074, p<0.0001, respectively). Goal attainment of HbA1c of <7% was achieved by week 24 in 35% (p=NS), 38% (p=0.0443), 41% (p=0.0133) for saxagliptin 2.5 mg, 5 mg, and 10 mg groups whereas placebo rate was 24%. PPG-AUC was reduced for saxagliptin at all doses versus placebo with statistical significance demonstrated for saxagliptin 5 mg (p=0.0002) and 10 mg (p<0.0001). Adverse event frequency was similar across all study arms. No cases of confirmed hypoglycemia (symptoms, with fingerstick glucose ≤50 mg/dL) were observed. Saxagliptin was not associated with weight gain.

A randomized, 24-week, phase 3, double-blind trial evaluated the efficacy and safety of saxagliptin added to a submaximal sulfonylurea dose in comparison to up titration of sulfonylurea monotherapy in patients with T2DM taking sulfonylurea monotherapy with inadequate glycemic control.[270] Initially, all patients received open-label glyburide 7.5 mg daily for 4 weeks. A total of 768 patients between 18 to 77 years of age with HbA1c screening value of 7.5% to 10% were randomized and treated with saxagliptin 2.5 or 5 mg in combination with glyburide 7.5 mg versus glyburide 10 mg monotherapy for 24 weeks. Blinded up titration glyburide was allowed in the glyburide-only arm to a maximum total daily dose of 15 mg. Results at 24 weeks indicated that 92% of glyburide-only patients were up titrated to a total daily glyburide dose of 15 mg. Saxagliptin 2.5 and 5 mg provided statistically significant adjusted mean decreases from baseline to week 24 versus up titrated glyburide in HbA1c (-0.54%, -0.64% versus +0.08%, respectively; both p<0.0001) and fasting plasma glucose (-7, -10 versus +1 mg/dL, respectively; p=0.0218 and p=0.002). The proportion of patients achieving an HbA1c < 7% was greater for saxagliptin 2.5 mg and 5 mg versus up titrated glyburide (22.4% and 22.8% versus 9.1%, respectively; both p<0.0001). Postprandial glucose area under the curve was reduced for saxagliptin 2.5 and 5 mg versus up titrated glyburide (both p<0.0001). Adverse event occurrence was similar

across all groups. Reported hypoglycemic events were not statistically significantly different for saxagliptin 2.5 and 5 mg versus up titrated glyburide (13.3% and 14.6% versus 10.1%, respectively).

A multicenter, randomized, double-blind, active-controlled, phase 3 trial evaluated the efficacy and safety of initial therapy with saxagliptin in combination with metformin versus saxagliptin monotherapy and metformin monotherapy in 1,306 treatment-naïve patients with diabetes mellitus type 2.[271] Patients enrolled in the study had HbA1c 8% to 12%. Patients were randomized to receive saxagliptin 5 mg or 10 mg with metformin 500 mg, saxagliptin 10 mg with placebo, or metformin 500 mg with placebo for 24 weeks. Metformin was titrated over the first 5 weeks to a maximum of 2,000 mg per day. The main outcome measure was change in HbA1c from baseline to week 24, and secondary outcomes included change from baseline to week 24 in fasting plasma glucose (FPG), proportion of patients achieving HbA1c <7%, and postprandial glucose area under the curve (PPG-AUC). Results indicated that, at week 24, saxagliptin combination therapy with metformin demonstrated statistically significant adjusted mean decreases versus saxagliptin 10 mg and metformin monotherapies in HbA1c (-2.5% and -2.5% versus -1.7% and -2%, all p<0.0001 versus monotherapy) and FPG (-60 mg/dL and -62 mg/dL versus -31 mg/dL and -47 mg/dL, both p<0.0001 versus saxagliptin 10 mg; p=0.0002 saxagliptin 5 mg + metformin versus metformin; p<0.0001 saxagliptin 10 mg + metformin versus metformin). The proportion of patients achieving an HbA1c < 7% was greater with combination therapy versus monotherapy (all p<0.0001). PPG-AUC was significantly reduced for saxagliptin combination therapies versus saxagliptin 10 mg and metformin monotherapies (all p<0.0001 versus monotherapy). Adverse event occurrence was similar across all groups, and hypoglycemic events were infrequent.

A randomized, double-blind, placebo-controlled, 24-week trial evaluated the safety and efficacy of saxagliptin as add-on therapy to metformin versus placebo in patients with T2DM.[272] Seven-hundred forty-three patients with inadequate glycemic control on metformin monotherapy were randomly assigned to either saxagliptin at 3 different doses (2.5 mg, 5 mg, or 10 mg once daily) or placebo as an adjunct to a stable dose of metformin (1,500-2,500 mg). Primary endpoint was HbA1c change from baseline to week 24, and secondary endpoints included change from baseline to week 24 in fasting plasma glucose (FPG), percentage of patients achieving HbA1c <7%, and changes in postprandial glucose area-under-the-curve (PPG-AUC). Results demonstrated that saxagliptin 2.5, 5, and 10 mg plus metformin demonstrated statistically significant adjusted mean decreases from baseline to week 24 versus the control group in HbA1c (all p<0.0001), FPG (all p<0.0001), and PPG-AUC (all p<0.0001). HbA1c reductions for saxagliptin 2.5 mg, 5 mg, and 10 mg groups were -0.59%, -0.69%, and -0.58% versus placebo group reporting an increase in HbA1c of 0.13%. The percentages of patients achieving HbA1c of <7% were 37%, 44%, and 44% for the saxagliptin 2.5 mg, 5 mg, and 10 mg groups compared to 17% for placebo (all p<0.0001). Incidence of hypoglycemic adverse events and weight reductions were similar between the 2 groups.

The efficacy and safety of saxagliptin plus a TZD in 565 patients with T2DM and inadequate glycemic control on TZD monotherapy were evaluated in a multicenter, randomized, double-blind, phase 3 study.[273] Patients had a baseline HbA1c of 7% to 10.5% while on pioglitazone 30 or 45 mg or rosiglitazone 4 mg or 8 mg for at least 12 weeks before screening. Patients were given saxagliptin 2.5 or 5 mg once daily or placebo plus a stable TZD dose for 24 weeks. The adjusted mean decreases in HbA1c versus placebo from baseline to week 24, the primary outcome parameter, was -0.66% (p=0.0007) for saxagliptin 2.5 mg and -0.94% (p<0.0001) for saxagliptin 5 mg compared to -0.3% with

placebo. The percentage of patients achieving HbA1c <7% was 42.2% (p=0.001), 41.8% (p=0.0013), and 25.6% for saxagliptin 2.5 mg plus TZD, 5 mg plus TZD, and placebo groups, respectively. Hypoglycemic events were similar across all groups.

A total of 455 patients with T2DM participated in a 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of saxagliptin in combination with insulin in patients with inadequate glycemic control (HbA1c ≥7.5% and ≤11%) on insulin alone (n=141) or on insulin in combination with a stable dose of metformin (n=314).[274] Patients entered the trial on intermediate- or long-acting (basal) insulin or premixed insulin. Short-acting insulins were included only if it was administered as part of premixed insulin. Following a single-blind, 4-week, lead-in period, patients received insulin (and metformin if applicable) and were then randomized to add-on therapy with either saxagliptin 5 mg or placebo. Add-on therapy with saxagliptin resulted in a significant HbA1c change from baseline to week 24 of -0.7% versus -0.3% for placebo (-0.4% adjusted mean difference from placebo, p<0.0001). Add-on therapy with saxagliptin also resulted in a significant 2-hour postprandial glucose change from baseline to week 24 of -27 mg/dL versus -4 mg/dL for placebo (-23 mg/dL adjusted mean difference from placebo, p<0.05). The percentage of patients who discontinued due to lack of glycemic control or who were rescued was 23% for saxagliptin versus 32% for placebo. In the saxagliptin group, the overall incidence of reported hypoglycemia was 18.4% versus 19.9% for placebo. However, the incidence of confirmed symptomatic hypoglycemia (finger stick blood glucose ≤50 mg/dL) was higher with saxagliptin at 5.3% versus placebo at 3.3%.

A total of 257 patients with T2DM participated in a 24-week, randomized double-blind, placebo-controlled trial.[275] Patients were to be on a stable combined dose of metformin ER or immediate-release (at maximum tolerated dose, with minimum dose for enrollment being 1,500 mg) and a sulfonylurea (at maximum tolerated dose, with minimum dose for enrollment being ≥ 50% of the maximum recommended dose) for at least 8 weeks prior to enrollment. Patients were randomized to either double-blind saxagliptin 5 mg once daily or placebo as add-on to metformin and a sulfonylurea at the same constant dose given during enrollment. Sulfonylurea dose could be down titrated once in the case of a major hypoglycemic event or recurring minor hypoglycemic events. Saxagliptin in combination with metformin plus a sulfonylurea provided significant improvements in HbA1c and PPG compared with placebo in combination with metformin plus a sulfonylurea (-0.7 versus -0.1 and -12 versus +5, respectively). Six percent of patients in the saxagliptin group discontinued for lack of glycemic control as compared to 5% in the placebo group. The change in fasting plasma glucose from baseline to week 24 was not statistically significant. The percentage of patients achieving an HbA1c <7% was 31% add-on saxagliptin compared to 9% with add-on placebo. Significance was not tested. The overall incidence of reported hypoglycemia was 10.1% for the saxagliptin group and 6.3% for the placebo group. Confirmed hypoglycemia was reported in 1.6% of patients treated with saxagliptin and in none of the patients treated with placebo.

saxagliptin (Onglyza) as add-on to dapagliflozin plus metformin

A 24-week, double-blind, placebo-controlled trial included 315 patients with T2DM with a baseline of HbA1c ≥ 7% to ≤ 10.5% while on metformin (≥ 1,500 mg per day).[276] Patients participated in a 16-week open-label, lead-in treatment phase, in which they received metformin and 10 mg dapagliflozin. Following the lead-in period, eligible patients were randomized to add-on saxagliptin 5 mg once daily (n=153) or placebo (n=162). The saxagliptin group had a statistically greater reduction in HbA1c compared to the placebo-group (difference, -0.4%; 95% CI, -0.5 to -0.2).

saxagliptin (Onglyza) and cardiovascular outcomes

The SAVOR TIMI-53 study, a randomized, double-blind, placebo-controlled phase 4, manufacturer-funded trial, evaluated CV outcomes with saxagliptin (5 mg daily or 2.5 mg daily in patients with an eGFR ≤ 50 mL/minute).[277] Patients (n=16,492) were followed for a mean of 2.1 years. The study found that, in patients with T2DM with a history of or at risk for CV events, saxagliptin had no effect on the primary efficacy endpoint of a composite of CV death, MI, or ischemic stroke (HR with saxagliptin, 1; 95% CI, 0.89 to 1.12; p=0.99 for superiority; p<0.001 for noninferiority). The study did show that the rate of hospitalization for heart failure (HF) was significantly increased (p=0.007) with saxagliptin. The study authors recommend further investigation of this increased rate of HF. Rates of adjudicated cases of acute and chronic pancreatitis were similar.

saxagliptin plus dapagliflozin (Qtern) as add-on to metformin

A 24-week, double-blind, active-controlled, parallel-group trial included 870 patients with T2DM with a baseline of HbA1c ≥ 7.5% to ≤ 10% while on metformin (≥ 1,500 mg per day).[278] Patients were on a stable dose of metformin for at least 8 weeks prior to randomization to either saxagliptin 5 mg + dapagliflozin 5 mg (n=290), saxagliptin 5 mg + placebo (n=291), or dapagliflozin 5 mg + placebo (n=289), all as add-on to baseline metformin. The addition of saxagliptin + dapagliflozin resulted in statistically significant decreases in HbA1c compared to adding either component alone (difference compared to saxagliptin alone, -0.32% [95% CI, -0.48 to -0.17]; difference compared to dapagliflozin alone, -0.4% [95% CI, -0.55 to -0.24]; p<0.0001 for both). A larger percentage of patients randomized to add-on saxagliptin + dapagliflozin achieved an HbA1c <7% (42.8% compared to 28.5% with saxagliptin alone [p=0.0018] and 21.8% with dapagliflozin alone [p>0.0001]).

saxagliptin plus dapagliflozin plus metformin ER (Qternmet XR)

Another 24-week double-blind, active-controlled study compared once daily saxagliptin 5 mg + dapagliflozin 10 mg coadministered with metformin XR (n=179) to either saxagliptin 5 (n=176) of dapagliflozin 10 mg (n=179) added to metformin in patients with inadequately controlled T2DM (HbA1c ≥ 8% to ≤ 12%).[279] The saxagliptin + dapagliflozin + metformin ER combination therapy resulted in statistically significant decreases in HbA1c compared to the addition to metformin of either component (saxagliptin or dapagliflozin) alone (difference of triple therapy compared to addition of saxagliptin only, -0.49% [95% CI, -0.7 to -0.27]; difference compared to addition of dapagliflozin only, -0.26% [95% CI, -0.47 to -0.05]; p<0.0001 for both). A larger percentage of patients randomized to saxagliptin + dapagliflozin + metformin XR achieved an HbA1c < 7%, but the difference compared to the other groups was not statistically significant.

saxagliptin/metformin ER (Kombiglyze XR)

No large scale clinical efficacy or safety studies have been conducted specifically with the fixed-dose combination of saxagliptin and metformin ER. The FDA approved once-daily saxagliptin and metformin ER based upon 2 phase 3 clinical trials evaluating the efficacy and safety of saxagliptin and metformin immediate release (IR) as separate tablets compared to placebo added to metformin IR tablets. Studies found that the 10 mg daily dose of saxagliptin does not provide greater efficacy than the 5 mg daily dose.

sitagliptin (Januvia)

The efficacy and safety of sitagliptin were evaluated in a randomized, double-blind study with 701 patients with T2DM who were on metformin and evaluated for 24 weeks.[280] Patients had a baseline HbA1c ≥7% to ≤ 10% and were on metformin 1,500 mg daily or more. Sitagliptin 100 mg daily or placebo was added. After 24 weeks, HbA1c were reduced by -0.65% by sitagliptin. Significantly more patients on sitagliptin (47%) achieved HbA1c of <7% compared to placebo (18.3%). Body weight decreased similarly in both groups. Sitagliptin was well tolerated. Another study of similar design with sitagliptin added to ongoing metformin therapy demonstrated similar reductions of HbA1c.[281]

A 30-week, randomized, double-blind, placebo-controlled trial evaluated the efficacy and safety of continuing sitagliptin during insulin glargine initiation (10 mg once daily) and titration (to target FBG 72 to 100 mg/dL) in 746 patients with inadequate glycemic control who were on stable doses of metformin (≥ 1,500 mg/day) with or without a sulfonylurea.[282] At week 30, the mean HbA1c reduction was greater with sitagliptin than placebo (adjusted mean difference, -0.4%; 95% CI, -0.6 to -0.3; p<0.001). An equal proportion of patients in each group achieved target FBG (273%). Insulin doses were also similar between the groups.

sitagliptin (Januvia) and cardiovascular outcomes

TECOS was a double-blind, evaluated the CV outcomes for sitagliptin in 14,671 patients with T2DM and CV disease.[283] Patients were randomized to sitagliptin 100 mg daily (or 50 mg daily if eGFR was ≥ 30 and < 50 mL/min/1.73m^2) or placebo.[**284**] After a median follow up of 3 years, the primary composite endpoint (CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina) occurred at similar rates (11.4% and 11.6%, respectively). A subanalysis revealed a similar finding for the primary composite outcome in 2,004 patients ≥ 75 years of age (HR, 1.1; [0.89 to 1.36]), death (HR, 1.05 [0.83 to 1.32]), HF hospitalization (HR, 0.99; [0.65 to 1.49]), or severe hypoglycemia (HR, 1.03; [0.62 to 1.71]).

sitagliptin (Januvia) versus dapagliflozin (Farxiga®) in patients with mild renal impairment

CompoSIT-R:[285,286] This study compared the efficacy of daily doses of sitagliptin 100 mg (n=307) and dapagliflozin (5 mg, titrated to 10 mg; n=306), a sodium-glucose cotransporter 2 (SGLT2) inhibitor, in patients with T2DM and HbA1c ≥ 7 to ≤ 9.5% and mild renal insufficiency (eGFR ≥ 60 to < 90 mL/min/1.73m^2). Patients were also treated with background metformin with or without a sulfonylurea. After 24 weeks, the least square mean difference between the groups in change from baseline in HbA1c was -0.15% (95% CI, -0.26 to -0.04; p=0.006), which met the prespecified criteria for noninferiority and superiority of sitagliptin over dapagliflozin. In addition, HbA1c < 7% was achieved by 43% of patients treated with sitagliptin and 27% treated with dapagliflozin. Postprandial (2-hour) glucose was similar between the groups. A review of adverse events was notable for a lower incidence of drug-related adverse events with sitagliptin compared with dapagliflozin. Serious adverse events were reported in 3.3% of patients in the sitagliptin group compared to 4.3% in the dapagliflozin group.

sitagliptin (Januvia), sitagliptin/metformin (Janumet) versus sitagliptin/metformin ER (Janumet XR)

The co-administration of sitagliptin and metformin immediate-release has been studied in patients with T2DM inadequately controlled on diet and exercise and in combination with other antidiabetic medications. There have been no clinical efficacy or safety studies conducted with fixed-dose combination products sitagliptin/metformin (Janumet), or sitagliptin/metformin ER to characterize effect on HbA1c reduction. Bioequivalence of sitagliptin/metformin to co-administered sitagliptin and metformin immediate-release tablets and of sitagliptin/metformin ER tablet to co-administered sitagliptin and metformin ER tablets has been demonstrated.

In a 24-week, double-blind, placebo-controlled, parallel-group study, 1,091 patients with T2DM and HbA1c 7.5% to 11% were randomized to sitagliptin 100 mg/metformin 1,000 mg, sitagliptin 100 mg/metformin 2,000 mg, metformin 1,000 mg immediate-release, or metformin 2,000 mg immediate-release in divided doses twice daily, sitagliptin 100 mg daily, or placebo.[287] The mean baseline HbA1c was 8.8%. The placebo-subtracted HbA1c changes from baseline were -2.07% (sitagliptin/metformin 2,000 mg), -1.57% (sitagliptin/metformin 1,000 mg), -1.30% (metformin 2,000 mg), -0.99% (metformin 1,000 mg), and -0.83% (sitagliptin 100 mg) ($p<0.001$ for comparisons versus placebo and for coadministration versus respective monotherapies). The percentage of patients achieving HbA1c <7% was 66% for sitagliptin/metformin 2,000 mg group ($p<0.001$ versus sitagliptin monotherapy and metformin 2,000 mg groups). The incidence of hypoglycemia was low (0.5% to 2.2%) across active treatment groups and not significantly different from that in the placebo group (0.6%).

sitagliptin (Januvia) versus saxagliptin (Onglyza)

Adult patients with T2DM (n=801) and an HbA1c of 6.5% to 10% on stable metformin doses (1,500-3,000 mg/day) were randomized to add-on saxagliptin 5 mg or sitagliptin 100 mg once daily for 18 weeks.[288] The adjusted mean changes in HbA1c following the addition of saxagliptin or sitagliptin to stable metformin therapy were -0.52% and -0.62%, respectively. The between-group difference was 0.09% (95% CI, - 0.01 to 0.20%), demonstrating noninferiority as defined as an upper limit of the 2-sided 95% CI of the HbA1c difference between treatments was <0.3%). Both treatments were generally well tolerated; incidence and types of adverse events were comparable between groups. Hypoglycemic events, mostly mild, were reported in approximately 3% of patients in each treatment group. Body weight declined by a mean of 0.4 kg in both groups.

sitagliptin (Januvia) versus glipizide (Glucotrol®)

Patients (n=1,172) were randomized in a double-blind manner to the addition of sitagliptin 100 mg or glipizide 5 mg (maximum of 20 mg) daily to metformin for 52 weeks in a noninferiority trial.[289] From a mean baseline HbA1c of 7.5%, changes from baseline were -0.67% at week 52 in both groups, confirming noninferiority. The proportions of patients achieving an HbA1c <7% were 63% (for sitagliptin) and 59% (for glipizide). The proportion of patients experiencing hypoglycemia was significantly higher with glipizide than with sitagliptin (32% versus 5%; $p<0.001$). Sitagliptin led to weight loss (-1.5 kg) compared with weight gain (+1.1 kg) with glipizide ($p<0.001$].

sitagliptin (Januvia) versus TZDs

Patients (n=273) on metformin were randomized in a double-blind manner to receive the addition of sitagliptin 100 mg, rosiglitazone 8 mg, or placebo once daily for 18 weeks.[290] Change in HbA1c from baseline was the primary endpoint. After 18 weeks, both active add-on therapies led to greater improvements in HbA1c from the mean 7.7% baseline: -0.73% for sitagliptin (p<0.001 versus placebo) and -0.79% for rosiglitazone compared with -0.22% for placebo (p<0.001 versus placebo for both). No significant difference was observed between the sitagliptin and rosiglitazone treatments (0.06%, 95% CI, -0.14 to 0.25). The percentage of patients achieving HbA1c <7% was 55% with sitagliptin, 63% with rosiglitazone, and 38% for placebo. Body weight increased from baseline with rosiglitazone (1.5 kg) compared with a reduction in weight with sitagliptin (-0.4 kg) and placebo (-0.9 kg). The difference in body weight between the sitagliptin and rosiglitazone groups was 1.9 kg (95% CI, 1.3-2.5), and the proportion of patients experiencing a >3 kg increase in body weight was 21% in the rosiglitazone group compared with 2% in both the sitagliptin and placebo groups. Both active treatments were generally well tolerated, with no increased risk of hypoglycemia or gastrointestinal adverse events compared with placebo.

sitagliptin (Januvia) as add-on to TZDs

The efficacy and tolerability of sitagliptin added to pioglitazone (Actos®) therapy were assessed in patients with T2DM and HbA1c >7% and <10% while receiving a stable dose of pioglitazone of 30 to 45 mg per day.[291] In a multicenter, randomized, double-blind, placebo-controlled, parallel-group study, patients (n=353) were randomized to receive sitagliptin 100 mg daily or placebo for 24 weeks. The primary efficacy endpoint was change from baseline in HbA1c at week 24. Mean baseline HbA1c was 8.1% in the sitagliptin group and 8% in the placebo group. After 24 weeks, sitagliptin added to pioglitazone therapy was associated with significant reductions in HbA1c (-0.70%; p<0.001) and fasting plasma glucose (FPG) (-17.7 mg/dL; p<0.001) compared with placebo. Mean HbA1c values at study endpoint were 7.2% and 7.8% in the sitagliptin and placebo groups, respectively, and the proportions of patients reaching a target HbA1c of <7% were 45.4% and 23%, respectively (p<0.001). Sitagliptin was generally well tolerated, with no increased risk of hypoglycemia compared with placebo.

sitagliptin plus ertugliflozin (components of Steglujan)

VERTIS SITA:[292] A 26-week, double-blind, placebo-controlled study was performed in 291 patients with T2DM who were not adequately controlled by diet and exercise (HbA1c, 8% to 10.5%) to determine the safety and efficacy of ertugliflozin in combination with sitagliptin. Patients not receiving hyperglycemic treatment for ≥ 8 weeks entered a 2-week, single-blind, placebo run-in period. After the placebo run-in period, patients were then randomized to ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo in combination with sitagliptin 100 mg once daily. The mean reduction of HbA1c relative to the placebo group was -1.2% (95% CI, -1.5 to -0.8; p<0.001) in the ertugliflozin 5 mg group and -1.2% (95% CI, -1.6 to -0.9; p<0.001) in the ertugliflozin 15 mg group. Patients in the ertugliflozin 5 mg group were 6.9 times as likely to achieve an HbA1c < 7% than patients in the placebo group (95% CI, 2.8 to 16.8; p<0.001) and patients in the ertugliflozin 15 mg group were 7.4 times as likely to achieve an HbA1c < 7% than patients in the placebo group (95% CI, 3 to 18.3; p<0.001). Patients in both ertugliflozin groups also had greater reductions in body weight compared to placebo with a difference in means of -2 kg (95% CI, -2.99 to -1.01; p<0.001) in patients taking ertugliflozin 5 mg + sitagliptin 100 mg and -2.1 kg (95% CI, -3.1 to -1.11; P<0.001) in patients taking ertugliflozin 15 mg + sitagliptin 100 mg.

sitagliptin plus ertugliflozin versus ertugliflozin versus sitagliptin, as add-on to metformin

VERTIS FACTORIAL:[293] A 26-week, double-blind, active-controlled study was performed in 1,233 patients with T2DM who were not adequately controlled (HbA1c, 7.5% to 11%) on metformin monotherapy (≥ 1,500 mg/day) to determine the safety and efficacy of ertugliflozin in combination with sitagliptin compared to the individual components. Participants were randomized to receive ertugliflozin 5 mg, ertugliflozin 15 mg, sitagliptin 100 mg, or coadministration of ertugliflozin/sitagliptin 5/100 mg or ertugliflozin/sitagliptin 15/100 mg once daily. At week 26, a -1.5% mean reduction of HbA1c was observed in patients taking ertugliflozin/sitagliptin 5/100 mg and 15/100 mg daily as compared to the individual agents ertugliflozin 5 mg (-1%), ertugliflozin 15 mg (-1.1%), and sitagliptin 100 mg (-1.1%) ($p<0.001$ for all comparisons). The percent of patients achieving an HbA1c < 7% was 26.4% in patients taking ertugliflozin 5 mg, 31.9% in patients taking ertugliflozin 15 mg, 32.8% in patients taking sitagliptin 100 mg, 52.3% in patients taking ertugliflozin/sitagliptin 5/100 mg, and 49.2% in patients taking ertugliflozin/sitagliptin 15/100 mg.

sitagliptin/metformin (Janumet) versus metformin

In a 24-week, randomized, double-blind, placebo-controlled study, 701 patients with T2DM participated to compare sitagliptin/metformin to metformin alone.[294,295] Patients already on metformin 1,500 mg per day or higher (n=431) were randomized after completing a 2-week, single-blind placebo run-in period. Patients on metformin and another antihyperglycemic agent (n=229) and patients not on any antihyperglycemic agents (off therapy for at least 8 weeks, n=41) were randomized after a run-in period of approximately 10 weeks of metformin monotherapy (at a dose of at least 1,500 mg per day). Patients were randomized to also receive either 100 mg of sitagliptin or placebo, administered once daily. Mean baseline HbA1c was 8% in both groups. HbA1c changes from baseline were -0.7% for sitagliptin/metformin and zero percent for placebo/metformin. The percentage of patients achieving an HbA1c <7% was 47% in the sitagliptin/metformin immediate-release group compared to 18% in the metformin immediate-release monotherapy group.

sitagliptin/metformin + rosiglitazone (Janumet + Avandia®) versus metformin + rosiglitazone (Avandia)

In a randomized, double-blind, placebo-controlled study, 278 patients with T2DM participated in a comparison of sitagliptin in combination with metformin and rosiglitazone. [296,297] Patients on dual therapy with metformin ≥1,500 mg/day and rosiglitazone ≥4 mg/day or with metformin ≥1,500 mg/day and pioglitazone ≥30 mg/day (switched to rosiglitazone ≥4 mg/day) entered a dose-stable run-in period of 6 weeks. Patients on other dual therapy were switched to metformin ≥1,500 mg/day and rosiglitazone ≥4 mg/day in a dose titration/stabilization run-in period of up to 20 weeks in duration. After the run-in period, patients with inadequate glycemic control (HbA1C 7.5% to 11%) were randomized 2:1 to the addition of either 100 mg of sitagliptin or placebo, administered once daily. Mean reduction in HbA1C at week 54 was 1% for patients treated with sitagliptin and -0.3% for patients treated with placebo.

GLP-1 Agonists

dulaglutide (Trulicity) versus metformin

AWARD-3: A 52-week double-blind study compared the efficacy and safety of monotherapy with dulaglutide or metformin in 807 patients inadequately treated (HbA1c ≥ 6.5% and ≤ 9.5%) with diet and exercise with or without 1 anti-diabetic agent used at submaximal dose.[298,299] Patients were randomized to dulaglutide 1.5 mg or 0.75 mg once weekly or metformin 1,500 to 2,000 mg/day. Other oral hypoglycemic agents were discontinued prior to lead-in period. Primary endpoint was change in HbA1c at week 26. Mean changes in HbA1c of -0.8%, -0.7% and -0.6% were reported for dulaglutide 1.5 mg and 0.75 mg and metformin, respectively. Dulaglutide 1.5 and 0.75 mg were considered superior to metformin ($p<0.025$ for both). A greater percentage of patients on dulaglutide reached HbA1c < 7% and ≤ 6.5% compared to metformin ($p < 0.05$ for all comparisons). No severe hypoglycemia was reported. Mean changes in body weight were similar across all groups. Nausea, vomiting, and diarrhea were common adverse effects, with similar incidence reported between dulaglutide and metformin.

dulaglutide (Trulicity) versus sitagliptin (Januvia) as add-on to metformin

AWARD-5: A 104-week placebo-controlled, double-blind, parallel-arm study randomized 1,098 patients to dulaglutide 1.5 mg or 0.75 mg once weekly, sitagliptin 100 mg/day, or placebo, all as add-on to metformin in patients with T2DM.[300] Primary endpoint was change in HbA1c at 52 weeks. The mean HbA1c changes were -1.10%, -0.87 %, and -0.39% for dulaglutide 1.5 mg, dulaglutide 0.75 mg, and sitagliptin, respectively ($p < 0.001$, both comparisons). No events of severe hypoglycemia were reported. Mean weight changes at 52 weeks were greater with dulaglutide 1.5 mg (-3.03 kg) and dulaglutide 0.75 mg (-2.60 kg) compared with sitagliptin (-1.53 kg) ($p < 0.001$, both comparisons).

dulaglutide (Trulicity) versus exenatide (Byetta) as add-on to metformin and pioglitazone

AWARD-1: This 52-week, placebo-controlled, parallel-arm study compared of the effects of dulaglutide and exenatide on glycemic control in 976 patients with T2DM not adequately controlled with metformin and pioglitazone.[301,302] Patients were randomized to dulaglutide 1.5 mg or 0.75 mg, exenatide 10 mcg twice daily, or placebo. Patients were also on metformin ≥ 1,500 mg/day and pioglitazone 30 to 45 mg/day. Treatment groups were open-label for exenatide, while all others were blinded. After 26 weeks, patients in the placebo treatment group were randomized to either dulaglutide 1.5 mg or 0.75 mg once weekly. Primary endpoint was change in HbA1c at week 26. Mean reduction in HbA1c was 1.5%, 1.3%, 1%, and 0.5% for dulaglutide 1.5 mg and 0.75 mg, exenatide and placebo, respectively ($p<0.01$ for all as compared to placebo). A greater percentage of patients achieved HbA1c < 7% with both dulaglutide doses than with exenatide or placebo (all $p<0.001$). At both time points of 26 and 52 weeks, incidence of hypoglycemia was reported less in patients receiving dulaglutide 1.5 mg as compared to exenatide. While both doses of dulaglutide resulted in weight loss, compared to placebo, the difference in weight as compared to exenatide was -0.2 kg for dulaglutide 1.5 mg and +1.3 kg for dulaglutide 0.75 mg.

dulaglutide (Trulicity) versus insulin glargine (Lantus) as add-on to metformin and glimepiride

AWARD-2: In a 78-week, open-label study effects on glycemic control in patients with T2DM of dulaglutide were compared with insulin glargine. Patients (n=807) were randomized to dulaglutide 1.5 mg or 0.75 mg once weekly, or insulin glargine once daily, all as add-on to maximally tolerated

doses of metformin and glimepiride. Dosages of insulin glargine were initiated at 10 units once daily and titrated to a target fasting glucose of < 100 mg/dL. Only 24% of patients on insulin glargine were titrated to goal at the 52-week primary endpoint. The dosage of insulin glargine could be reduced or discontinued if persistent hypoglycemia occurred. At 52 weeks, reductions in HbA1c were 1.1%, 0.8%, and 0.6% for dulaglutide 1.5 mg and 0.75 mg, and insulin glargine, respectively. Dulaglutide resulted in an overall weight loss, while insulin glargine resulted in a weight gain. Mean difference in body weight as compared to insulin glargine was -1.9 kg for dulaglutide 1.5 mg and -1.3 kg for dulaglutide 0.75 mg.

dulaglutide (Trulicity) versus insulin glargine (Lantus) as add-on to insulin lispro (Humalog)

AWARD-4: This 52-week, open-label study compared dulaglutide and insulin glargine, in 884 type 2 diabetic patients on 1 or 2 insulin injections per day.[303] At randomization, patients discontinued their previous insulin regimens and were assigned to dulaglutide 1.5 mg or 0.75 mg once weekly, or insulin glargine once daily, all in combination with prandial insulin lispro 3 times daily with or without metformin. Insulin lispro was titrated in each arm based on preprandial and bedtime glucose, and insulin glargine was titrated to a fasting plasma glucose goal of <100 mg/dL. Mean reduction in HbA1c at week 26 was 1.6% for each dulaglutide dose and 1.4% for insulin glargine. Mean change in body weight was +0.2 kg for dulaglutide 0.75 mg, -0.9 kg for dulaglutide 1.5 mg, and +2.3 kg for insulin glargine.

dulaglutide (Trulicity) versus liraglutide (Victoza) as add-on to metformin

AWARD-6: In this open-label, parallel-arm study the efficacy of dulaglutide was compared to liraglutide in 599 patients with T2DM who were also on metformin.[304] Patients were randomized to dulaglutide 1.5 mg once weekly or liraglutide 1.8 mg once daily. At week 26, mean reduction in HbA1c was 1.42% for dulaglutide and 1.36% for liraglutide, resulting in noninferiority of dulaglutide compared to liraglutide. No severe hypoglycemia was reported. Gastrointestinal adverse events were reported similarly in both treatment groups.

dulaglutide (Trulicity) versus insulin glargine (Lantus) in patients with renal impairment

AWARD 7:[305] A 52-week, open-label, parallel-arm study compared dulaglutide with insulin glargine in patients with T2DM and moderate or severe chronic kidney disease. Baseline HbA1c was 7.5% to 10.5%. Patients were randomized to once-weekly dulaglutide (1.5 mg or 0.75 mg) or daily insulin glargine; all study treatments were in combination with insulin lispro. The primary outcome was change in HbA1c from baseline at 26 weeks. Both doses of dulaglutide were determined to be noninferior to insulin glargine (difference -0.05% [95% CI -0.26 to 0.15, p<0.0001] with dulaglutide 1.5 mg and 0.02% [-0.18 to -0.22, p=0.0001] with dulaglutide 0.75 mg). Effects were durable through week 52. At 52 weeks, the effect of dulaglutide on the secondary endpoint of urine albumin-to-creatinine ratio (UACR) was not significantly different from that of insulin glargine (least square mean -22.5% [95% CI, -35.1 to -7.5] with dulaglutide 1.5 mg; -20.1% [-33.1 to -4.6] with dulaglutide 0.75 mg; -13% [-27.1 to 3.9] with insulin glargine). Dulaglutide was associated with a higher incidence of nausea and diarrhea and lower incidence of symptomatic hypoglycemia compared to insulin glargine. ESRD was reported in 4% and 7% of patients on dulaglutide 1.5 mg and 0.75 mg, respectively, and in 8% of patients on insulin glargine.

AWARD-10: Patients in a 24-week, double-blind, parallel-arm study (n=424) with inadequately controlled T2DM (HbA1c ≥ 7% to ≤ 9.5%) while on stable doses of an SLGT2 inhibitor, with or without metformin, were randomized to addition of dulaglutide or placebo. At 24 weeks, a greater reduction in HbA1c was seen with dulaglutide than with placebo; the least square mean differences compared to placebo with dulaglutide 1.5 mg was -0.79% (95% CI, -0.7 to -0.61) and for dulaglutide 0.75 mg was -0.66% (95% CI, -0.84 to -0.49). Severe hypoglycemia was reported in 1 patient treated with dulaglutide 0.75 mg.

dulaglutide (Trulicity) in combination with an SGLT2 inhibitor

A 24-week, double-blind, placebo-controlled trial evaluated the addition of dulaglutide 0.75 mg or 1.5 mg in patients on SGLT2 inhibitor therapy with or without metformin.[306] At week 24, both doses of dulaglutide led to a statistically significant HbA1c reduction (mean difference from placebo for each dose, -0.7 [95% CI, -0.8 to -0.5] and -0.8 [95% CI -0.9 to -0.6], respectively; p<0.01 for both).

exenatide (Byetta) as add-on to sulfonylurea

A triple-blind, placebo-controlled, multicenter, 30-week study evaluated exenatide in patients with T2DM who had inadequate treatment with sulfonylureas.[307] Average HbA1c was 8.6% at baseline, and were comparable across treatment arms. After a 4-week, single-blind, placebo lead-in period, 377 subjects were randomized and began 4 weeks of 5 mcg subcutaneous exenatide (treatment arms A and B) or placebo twice daily. The dose of exenatide in the active treatment arm B increased to 10 mcg twice daily after 4 weeks. All subjects continued sulfonylurea therapy. At week 30, HbA1c changes from baseline were -0.86%, -0.46%, and +0.12% in the exenatide 10 mcg, 5 mcg, and placebo arms, respectively (adjusted p<0.001). Of evaluable subjects with baseline HbA1c > 7% (n=237), 41% (exenatide 10 mcg), 33% (exenatide 5 mcg), and 9% (placebo) achieved HbA1c ≤ 7% (p<0.001). Patients in the exenatide arms had dose-dependent progressive weight loss, with an end-of-study loss in the 10 mcg exenatide arm of -1.6 kg from baseline (p<0.05 versus placebo). Weight loss in the 5 mcg arm was not statistically different than the placebo arm. Adverse events were generally mild or moderate and primarily gastrointestinal. There were no cases of severe hypoglycemia. Another study of similar design with 336 patients found similar results when using exenatide in combination with metformin alone.[308] Some authors credited with the publications have been involved with manufacturer-funded studies of exenatide.

exenatide (Byetta) as add-on to metformin and sulfonylurea

A double-blind, placebo-controlled study of 733 patients with T2DM and inadequate glycemic control with combined metformin-sulfonylurea therapy, found comparable results at 30 weeks using the same treatment arms as the above study.[309] At week 30, HbA1c changes from baseline were -0.8% (exenatide 10 mcg), -0.6% (exenatide 5 mcg), and +0.2% (placebo, adjusted p<0.0001 versus placebo). Placebo-adjusted reductions were -1% for exenatide 10 mcg and -0.8% for exenatide 5 mcg groups. In the evaluable population, exenatide-treated patients were more likely to achieve HbA1c ≤ 7% than placebo-treated patients (34%, exenatide 10 mcg group; 27%, exenatide 5 mcg group; and 9%, placebo; p<0.0001). Weight loss occurred in both exenatide treated groups (-1.6 kg, p≤0.01 versus placebo). Mild or moderate nausea was the most frequently reported adverse event. Hypoglycemia was reported in 28% of exenatide 10 mcg group, 19% of exenatide 5 mcg group, and 13% of the placebo group.

exenatide (Byetta) as add-on to insulin glargine (Lantus)

In a 30-week, double-blind, placebo-controlled trial, adults with T2DM and an HbA1c level of 7.1% to 10.5% who were receiving insulin glargine alone or in combination with metformin and/or pioglitazone were randomized to receive exenatide (5 mcg twice daily for 4 weeks and 10 mcg twice daily thereafter) or placebo.[310] At randomization, participants (n=261) with HbA1c levels > 8.0% continued to receive their current dose of insulin glargine; those with HbA1c ≤ 8.0% decreased their dose by 20%. Insulin glargine doses were maintained for 5 weeks, after which doses were titrated to achieve a fasting glucose level < 100 mg/dL. The HbA1c level decreased by 1.74% in the exenatide group and by 1.04% in the placebo group (p<0.001). At 30 weeks, the proportion of participants that achieved HbA1c ≤ 7.0% was 60% in the exenatide group and 35% in the placebo group. Average increases in insulin dosage with exenatide and placebo were 13 U/d and 20 U/d, respectively. Weight decreased by 1.8 kg with exenatide and increased by 1.0 kg with placebo. The estimated rate of minor hypoglycemia was similar in both groups. Rates of nausea, diarrhea, vomiting, headache, and constipation were higher with exenatide than with placebo. Thirteen exenatide patient and 1 placebo patient discontinued due to adverse events (p<0.010).

exenatide (Byetta) versus insulin glargine (Lantus)

In a 26-week multicenter, open-label, randomized, controlled trial, 551 patients with T2DM and inadequate glycemic control despite combination metformin and sulfonylurea therapy were randomized to treatment with exenatide 10 mcg twice daily or insulin glargine once daily.[311] At week 26, both exenatide and insulin glargine reduced HbA1c levels by 1.11%. Insulin glargine reduced fasting glucose concentrations more than exenatide. Body weight decreased 2.3 kg with exenatide and increased 1.8 kg with insulin glargine. Rates of symptomatic hypoglycemia were similar, but nocturnal hypoglycemia occurred less frequently with exenatide (0.9 events/patient-year versus 2.4 events/patient-year). Nausea (57.1% versus 8.6%), vomiting (17.4% versus 3.7%), and diarrhea (8.5% versus 3%) were more common in the exenatide group than in the insulin glargine group.

A randomized, open-label, crossover, noninferiority study compared the efficacy of exenatide 10 mcg twice daily and insulin glargine once daily for 16 weeks in patients (n=138) with T2DM inadequately controlled with metformin or a sulfonylurea monotherapy.[312] The primary outcome variable was the change in HbA1c. Secondary outcomes included the proportion of patients achieving HbA1c of < 7%, the change in fasting plasma glucose (FPG), and change in body weight. Both exenatide and insulin glargine were associated with similar significant changes from baseline (mean HbA1c 8.95%) in HbA1c (both -1.36%; p<0.001 versus baseline). Similar proportions of patients achieved HbA1c < 7% (37.5 and 39.8%, respectively; p=NS). Patients lost weight during exenatide treatment, whereas they gained weight during insulin glargine treatment; (mean difference, -2.2 kg; p<0.001). Both exenatide and insulin glargine were associated with significant reductions from baseline in FPG, although the reduction was significantly greater with insulin glargine compared with exenatide (mean difference, 1.2 mmol/L; p<0.001). The percentages of patients reporting nausea during exenatide and insulin glargine treatment were 42.6 and 3.1%, respectively; the incidence of hypoglycemia was 14.7 and 25.2%, respectively (p=NS).

exenatide ER (Bydureon) as add-on to insulin glargine (Lantus)

DURATION 7:[313] A double-blind study included 464 patients with inadequately controlled T2DM (HbA1c of 7% to 10.5%) while on insulin glargine (≥ 20 units/day), with or without metformin (≥ 1,500 mg/day) and/or a sulfonylurea. Patients were randomized to receive add-on therapy with exenatide ER or placebo. At 28 weeks, the exenatide ER group experienced a significantly greater reduction in HbA1c compared to the placebo group (least square mean [LSM] difference was -0.73%; 95% CI, -0.93%, -0.53%; p<0.001). The LSM difference in fasting plasma glucose with exenatide ER compared to placebo was -0.53 (95% CI, -0.99, -0.06; p=0.28). Significantly more patients treated with exenatide ER achieved HbA1c < 7% compared to those on placebo (32.5% versus 7.4%, respectively). Gastrointestinal adverse effects and injection site reactions were reported more often with exenatide ER.

exenatide ER (Bydureon) plus dapagliflozin (Farxiga) as add-on to metformin

DURATION-8:[314] In a 28-week, double-blind, active-controlled, multicenter, phase 3 trial, a total of 695 adult patients with inadequately controlled T2DM on metformin (≥ 1,500 mg/day) were randomized 1:1:1 to once-daily oral dapagliflozin 10 mg plus once-weekly exenatide SC 2 mg, dapagliflozin with exenatide-matched placebo, or exenatide with dapagliflozin-matched oral placebo, all as add-on to background metformin. The primary endpoint was change in HbA1c from baseline to week 28. Exenatide ER plus dapagliflozin significantly reduced HbA1c from baseline compared with exenatide ER alone (-0.4% [95% CI, -0.6 to -0.1]; p=0.004) or dapagliflozin alone (-0.6% [95% CI, -0.8 to -0.3]; p<0.001). The combination of dapagliflozin plus exenatide was also superior to either drug alone for all secondary efficacy endpoints, including reductions in fasting plasma and postprandial glucose, more patients who achieved HbA1c < 7%, weight loss, a greater proportion of patients with weight loss of ≥ 5%, and reductions in systolic blood pressure (all p≤0.025). There were no reports of major or minor hypoglycemia. The most common adverse effects reported were diarrhea, injection-site nodules, nausea, and urinary tract infection.

exenatide ER (Bydureon) versus exenatide (Byetta)

DURATION-1:[315] A 30-week, randomized, open-label, noninferiority study compared exenatide ER 2 mg administered once weekly to exenatide 10 mcg administered twice a day, in 295 patients with T2DM (HbA1c 8.3%, mean fasting plasma glucose 9 mmol/L, and weight 102 kg [SD 20]). The patients were naïve to drug therapy, or on 1 or more oral antidiabetic agents. The primary endpoint was the change in HbA1c at 30 weeks. Patients on exenatide once a week had significantly greater changes in HbA1c than patients on exenatide twice a day (-1.9 versus -1.5, 95% CI -0.54 to -0.12; p=0.0023). More patients on the once a week agent versus twice a day achieved target HbA1c levels of 7% or less (77% once weekly exenatide versus 61% twice daily exenatide, p=0.0039). In an open-label extension of the DURATION 1 study, 258 patients either continued or were switched to exenatide ER 2 mg once weekly for an additional 22 weeks.[316] Patients that continued exenatide ER maintained HbA1c through 52 weeks (-2.0% [-2.1 to -1.8%], LS mean [95%CI]). Patients that switched from twice daily exenatide to weekly exenatide ER experienced further reductions in HbA1c; however, both groups reported the same HbA1c reduction and mean HbA1c at week 52. There was no increased risk of hypoglycemia and similar reductions in body weight reported with exenatide ER. In addition, in 153 patients who completed 5 years of treatment, HbA1c remained significantly reduced compared to baseline and no new safety signals were observed with once weekly exenatide treatment.[317]

DURATION-5[318,319]: A 24-week, randomized, open-label trial compared the safety and efficacy of exenatide extended-release (ER) 2 mg weekly to exenatide 10 mcg twice daily in addition to existing oral antidiabetic agents. Subjects (n=252) included patients with T2DM and inadequate glycemic control with diet and exercise alone or with oral antidiabetic therapy, including metformin, a sulfonylurea, a thiazolidinedione, or combination of 2 of those therapies. The mean baseline HbA1c was 8.4%. The mean change in HbA1c (%) at week 24 was -1.6 for exenatide ER and -0.9 for exenatide. Adverse reactions reported were nausea, diarrhea, and injection site erythema in 14, 9.3, and 5.4% of subjects treated with exenatide ER, respectively and 35, 4.1, and 2.4% of subjects treated with exenatide, respectively. No major incidence of hypoglycemia was reported.

exenatide ER (Bydureon) versus liraglutide (Victoza)

DURATION 6:[320] In a 26 week, open-label, parallel-group study 912 patients aged 18 years or older with T2DM treated with lifestyle modification and oral antihyperglycemic drugs were randomly assigned to receive injections of once-daily liraglutide (1.8 mg) or once-weekly exenatide (2 mg). The change in HbA1c from baseline to week 26 was greater in patients in the liraglutide group than in those in the exenatide group (-1.48% versus -1.28%; 95% CI 0.08% to 0.33%). Decreases in body weight were reported in both groups, but greater decreases were found with liraglutide (mean -2.68 kg for exenatide ER [95%CI -3.0 to -2.32] and mean -3.57 kg for liraglutide [95%CI -3.94 to -3.21]). The most common adverse events were nausea (21% in the liraglutide group versus 9% in the exenatide group), diarrhea (13% versus 6%, respectively), and vomiting (11% versus 4%, respectively), which occurred less frequently in the exenatide group and with decreasing incidence over time in both groups.

exenatide ER (Bydureon) versus sitagliptin (Januvia) or pioglitazone as add-on to metformin

DURATION-2:[321] In a 26-week double-blind, double-dummy, superiority trial, patients with uncontrolled T2DM with metformin were randomized to exenatide ER 2 mg injected once weekly (n=170), oral sitagliptin 100 mg once daily (n=172), or oral pioglitazone 45 mg once daily (n=172); all groups received matching placebo. The HbA1c decreased significantly more with exenatide compared to sitagliptin or pioglitazone; treatment differences were -0.6% (95% CI, -0.9 to -0.4; p<0.0001) for exenatide versus sitagliptin, and -0.3% (95% CI, -0.6 to -0.1; p=0.0165) for exenatide versus pioglitazone. Weight loss with exenatide was also significantly greater than the other agents; difference versus sitagliptin was -1.5 kg (95% CI, -2.4 to -0.7; p=0.0002); difference versus pioglitazone was -5.1 kg (95% CI, -5.9 to -4.3; p<0.0001). No events of major hypoglycemia were reported. The most frequent adverse events with exenatide and sitagliptin were nausea (24% and 10%, respectively) and diarrhea (18% and 10%, respectively); upper-respiratory-tract infection (10%) and peripheral edema (8%) were the most frequent events with pioglitazone.

exenatide ER autoinjector (Bydureon BCise) versus sitagliptin (Januvia)

DURATION-NEO-2:[322] This 28-week, open-label, multicenter study randomized (3:2:1) 365 patients with uncontrolled T2DM on metformin monotherapy to exenatide ER 2 mg SC once weekly, sitagliptin 100 mg orally once daily, or oral placebo. At 28 weeks, significantly greater reduction in HbA1c was seen with exenatide ER compared to sitagliptin (-1.13% versus -0.75%; p=0.02) and placebo (-0.4%; p=0.001). A greater proportion of patients treated with exenatide ER achieved HbA1c < 7% than those treated with sitagliptin (43.1% versus 32%; p<0.05) or placebo (43.1% versus 24.6%; p<0.05). Both exenatide ER and sitagliptin reduced fasting plasma glucose from baseline (-21.3 and -11.3 mg/dL;

respectively) compared to placebo (+9.6 mg/dL); difference between exenatide ER and sitagliptin was not significant. A decrease in body weight was reported with exenatide ER (--.12 kg) and sitagliptin -1.19 kg), while an increase was seen with placebo (+0.15 kg).

exenatide ER (Bydureon, Bydureon BCise) and cardiovascular outcomes

EXSCEL:[323] A total of 14,752 patients with T2DM, with or without CVD were randomized to exenatide ER SC 2 mg once-weekly or matching placebo (73.1% had previous CVD). Median follow-up was 3.2 years. The primary composite outcome of first occurrence of CV death, nonfatal MI, or nonfatal stroke occurred in 11.4% of patients in the exenatide group and 12.2% in the placebo group (HR, 0.91; 95% CI, 0.83 to 1). Exenatide was noninferior, but not superior, to placebo in the intent-to-treat analysis. Rates of individual primary and secondary endpoint components of CV death, MI, stroke, hospitalization for heart failure, and hospitalization for ACS were similar between the groups.

liraglutide (Victoza) versus glimepiride

LEAD-3[324]: In this 52-week, controlled trial 746 patients with T2DM were randomized to once daily liraglutide 1.2 mg or 1.8 mg or glimepiride 8 mg. The primary outcome was change in HbA1c. HbA1c decreased by 0.51% with glimepiride versus 0.84% with liraglutide 1.2 mg (difference -0.33%; 95% CI, -0.53 to -0.13, p<0.05) and 1.14% with liraglutide 1.8 mg (difference -0.62%; 95% CI, -0.83 to -0.42, p<0.0001). No events of major hypoglycemia occurred. Five patients discontinued therapy due to vomiting in the liraglutide 1.2 mg group, 1 patient in 1.8 mg group, and 0 patients in the glimepiride group. Discontinuations due to ineffective therapy were 3.6% in the liraglutide 1.8 mg group, 6% in the liraglutide 1.2 mg group, and 10.1% in the glimepiride group. Liraglutide 1.8 and 1.2 mg resulted in 2.5 and 2.1 kg weight loss, respectively (p<0.0001) compared to a 1.1 kg weight gain with glimepiride.

liraglutide (Victoza) versus glimepiride as add-on to metformin

LEAD-2[325]: A 26-week controlled trial randomized 1,091 patients to liraglutide 0.6 mg, 1.2 mg, 1.8 mg, placebo, or glimepiride 4 mg, all as add-on to metformin up to 2,000 mg per day. HbA1c increased by 0.1% with placebo/metformin, decreased by 1% with glimepiride/metformin, decreased by 1% in both liraglutide 1.2 mg and 1.8 mg groups (p<0.0001 for the liraglutide groups). Discontinuations due to ineffective therapy were 5.4% in the liraglutide 1.8 mg/metformin group, 3.3% in the liraglutide1.2 mg/metformin group, 23.8% in the placebo/metformin group, and 3.7% in the glimepiride/metformin group. The liraglutide 1.8 mg/metformin and liraglutide 1.2 mg/metformin groups had a weight loss of 2.8 and 2.6 kg, respectively (p<0.05) compared to a 1.5 kg decrease in the placebo/metformin and 1 kg increase in the glimepiride/metformin groups.

liraglutide (Victoza) versus rosiglitazone as add-on glimepiride

LEAD-1[326]: This was a 26-week controlled trial of 1,041 patients randomized to liraglutide 0.6 mg, 1.2 mg, 1.8 mg, placebo, or rosiglitazone 4 mg, all as add-on to glimepiride 4 mg (the dose of glimepiride could be reduced by the investigator). Liraglutide 1.2 or 1.8 mg resulted in greater reductions in HbA1c (-1.1% each, p<0.0001), compared with placebo (+0.2%, p<0.0001) or rosiglitazone (-0.4%, p<0.0001) when added to glimepiride. Changes in body weight observed were: liraglutide 1.8 mg (-0.2 kg), liraglutide 1.2 mg (+0.3 kg), placebo (-0.1 kg), and rosiglitazone (+2.1 kg, p<0.0001). Main adverse events for all treatments were minor hypoglycemia (< 10%), nausea (< 11%), vomiting (< 5%), and diarrhea (<8%). The percentage of patients who discontinued due to ineffective therapy was 3% in

the liraglutide 1.8 mg/glimepiride group, 3.5% in the liraglutide 1.2 mg/glimepiride group, 17.5% in the placebo/glimepiride group, and 6.9% in the rosiglitazone/glimepiride group.

liraglutide (Victoza) versus insulin glargine (Lantus) as add-on metformin and glimepiride

LEAD-5[327]: In a 26-week study of 581 patients randomized to liraglutide 1.8 mg, placebo, or insulin glargine open-label arm (dose could be adjusted), all as add-on to metformin 2,000 mg or glimepiride 4 mg. The liraglutide group resulted in 1.3% decrease (p<0.0001) in HbA1c compared to 0.2% decrease with placebo, and 1.1% decrease in the insulin group. The difference in HbA1c for insulin glargine is within the predefined noninferiority margin. Body weight was reduced by 1.8 kg in the liraglutide group and increased by 1.6 kg in the insulin group. Rates of hypoglycemic episodes (major, minor, and symptoms only, respectively) were 0.06, 1.2, and 1 events/patient/year, respectively, in the liraglutide group (compared with 0, 1.3, 1.8 events/patient/year, and 0, 1, 0.5 events/patient/year with insulin and placebo, respectively). A higher number of adverse events, including 14% nausea, were reported with liraglutide. Discontinuation percentages due to ineffective therapy were 0.9% in the liraglutide 1.8 mg group, 0.4% in the insulin glargine group, and 11.3% in the placebo group.

liraglutide (Victoza) as add-on to metformin and rosiglitazone

LEAD-4: This was a 26-week controlled trial of 533 patients randomized to liraglutide 1.2 mg, 1.8 mg, or placebo, all as add-on to rosiglitazone 8 mg plus metformin 2,000 mg. HbA1c significantly decreased by 1.5% in each of the liraglutide groups compared to a 0.5% decrease in the placebo group.[328] Dose-dependent weight loss occurred with liraglutide 1.2 mg and 1.8 mg groups (1 kg and 2 kg, respectively [p<0.0001]) compared with weight gain with placebo (0.6 kg). Minor hypoglycemia was reported more frequently with liraglutide, but no major hypoglycemia occurred. Gastrointestinal (GI) adverse events were more common with liraglutide; however, most GI events occurred early in therapy and were transient. Discontinuation percentages due to ineffective therapy were 1.7% in the liraglutide 1.8 mg group, 1.7% in the liraglutide 1.2 mg group, and 16.4% in the placebo group.

liraglutide (Victoza) versus exenatide (Byetta) as add-on to metformin and/or sulfonylurea

LEAD-6 versus exenatide: In a 26–week, open-label trial, 464 patients with inadequately controlled T2DM on maximally-tolerated doses of metformin, sulfonylurea, or both, were stratified by previous oral antidiabetic therapy and randomized to once daily liraglutide 1.8 mg or exenatide 10 mcg twice daily.[329,330] Patients randomized to exenatide started on a dose of 5 mcg twice-daily for 4 weeks and then were escalated to 10 mcg twice daily. Compared with exenatide, liraglutide 1.8 mg resulted in significantly greater reductions in HbA1c (-1.1% versus -0.8%; 95% CI, −0.47 to −0.18; p<0.0001) and more patients achieved an HbA1c value of < 7% (54% versus 43%, respectively; odds ratio 2.02; 95% CI, 1.31 to 3.11; p=0.0015). Liraglutide also reduced mean FPG more than exenatide (−1.61 versus −0.60 mmol/L; 95% CI, −1.37 to −0.65; p<0.0001) but PPG control was less effective after breakfast and dinner. Both drugs were well tolerated, but nausea was less persistent (p<0·0001) and minor hypoglycemia (p=0.0131) less frequent with liraglutide than with exenatide. Two patients taking both exenatide and a sulfonylurea had a major hypoglycemic episode. Both treatment groups had a mean decrease from baseline in body weight of approximately 3 kg.

liraglutide (Victoza) versus sitagliptin (Januvia) as add-on to metformin

In a 26-week parallel-group, open-label trial, adult subjects with T2DM who had inadequate glycemic control on metformin were randomized to receive liraglutide 1.2 mg (n=225) or 1.8 mg (n=221) subcutaneous once daily, or sitagliptin 100 mg oral once daily (n=219).[331] The primary endpoint was change in HbA1c from baseline to week 26. Mean HbA1c was reduced to a greater extent with liraglutide 1.8 mg (-1.5%, 95% CI -1.63 to -1.37) and 1.2 mg (-1.24%, -1.37 to -1.11) than sitagliptin (-0.9%, -1.03 to -0.77). Estimated mean treatment differences for liraglutide versus sitagliptin were -0.6% (95% CI -0.77 to -0.43, p<0.0001) for 1.8 mg and -0.34% (-0.51 to -0.16, p<0.0001) for 1.2 mg liraglutide. Nausea was more common with both doses of liraglutide (27% and 21%) than with sitagliptin (5%). Minor hypoglycemia was similar in all treatment groups. Participants continued their same treatment regimen in a 26-week extension study. At week 52, mean reductions in HbA1c from baseline were similar to those reported at week 26; liraglutide 1.2 mg (−1.29% [95% CI: −1.43 to −1.15]), 1.8 mg (−1.51% [−1.65 to −1.37]), and sitagliptin (−0.88% [−1.02 to −0.74]). Estimated mean treatment differences were −0.4% (95% CI −0.59 to −0.22) for liraglutide 1.2 mg versus sitagliptin and −0.63% (−0.81 to −0.44) for liraglutide 1.8 mg versus sitagliptin (p<0.0001 for both doses).[332] During the extension phase, report rates of nausea did not differ significantly between liraglutide (1.2 or 1.8 mg) and sitagliptin treatment groups.

liraglutide (Victoza) as add-on to metformin and sequential intensification with basal insulin detemir (Levemir®)

A randomized, open-label study evaluated the addition of liraglutide to metformin followed by intensification of insulin detemir in 988 patients with T2DM uncontrolled on metformin with or without sulfonylurea.[333] Sulfonylurea was discontinued and injectable liraglutide (1.8 mg/day) was added for 12 weeks as the run-in phase. Subsequently, those with HbA1c ≥7 % were randomized to 26 weeks open-label addition of insulin detemir to metformin plus liraglutide or continued without insulin detemir. Patients achieving HbA1c <7% continued unchanged treatment (observational arm). The primary endpoint was A1C change between randomized groups. Of the patients completing the run-in, 61% achieved HbA1c <7% (mean change -1.3% from 7.7% at start), whereas 39% did not (-0.6% from 8.3% at start). During run-in, 17% withdrew; 46% of these due to gastrointestinal adverse events. At week 26, HbA1c decreased further, by 0.5% (from 7.6 % at randomization) with insulin detemir versus 0.02% increase without insulin detemir to 7.1% and 7.5%, respectively (estimated treatment difference -0.52 [95% CI -0.68 to -0.36]; p<0.0001). A total of 43% of patients with insulin detemir versus 17% without reached HbA1c <7%. Mean weight decreased by 3.5 kg during run-in, then by 0.16 kg with insulin detemir or 0.95 kg without insulin detemir. Hypoglycemia occurred at very low rates.

liraglutide (Victoza) use in pediatric patients

Safety and efficacy of liraglutide was evaluated in a 26-week, double-blind, parallel-group, placebo-controlled trial (NCT01541215) in 134 pediatric patients ≥ 10 years of age with T2DM.[334,335] Patients were randomized to once daily liraglutide or placebo in combination with metformin with or without basal insulin. At baseline, all patients were on a metformin dose of 1,000 to 2,000 mg and the basal insulin dose was reduced by 20%. Liraglutide doses were titrated by 0.6 mg on a weekly basis for 2 to 3 weeks, up to 1.8 mg per day. At 26 weeks, liraglutide demonstrated superiority over placebo in HbA1c reduction (estimated difference, -1.06%; 95% CI, -1.65 to -0.46; p<0.001). In a 26-week, open-label

extension phase, the estimated difference in HbA1c was -1.3%. At both time points, FPG decreased with liraglutide and increased with placebo.

liraglutide (Victoza) and cardiovascular outcomes

LEADER[336]: A double-blind trial randomized 9,340 patients with T2DM and high CV risk to liraglutide 1.8 mg daily (or the maximum tolerated dose) or placebo. Patients were followed over a median of 3.8 years. Liraglutide was associated with a significant 13% relative reduction (RR) in the first occurrence of a major coronary event (death from CV cause, nonfatal myocardial infarction [MI], or nonfatal stroke) as compared to placebo. While the rate of death from CV or other causes was lower with liraglutide (22% and 15% RR, respectively), the rates of nonfatal MI, nonfatal stroke, and hospitalization for HF were not statistically significantly lower than reported with placebo.

liraglutide/insulin degludec (Xultophy) versus placebo

A 26-week, double-blind, placebo-controlled trial (NCT01618162) evaluated the safety and efficacy of liraglutide/insulin degludec in 435 patients with T2DM inadequately controlled on a sulfonylurea with or without metformin.[337] Liraglutide/insulin degludec was initiated at a dose of 10 units and was titrated to maintain FPG of 72 to 108 mg/dL. Background sulfonylurea and metformin were continued. At week 26, the difference in least square mean change in HbA1c between the groups was -0.81% (95% CI, -0.98 to -0.63) favoring liraglutide/insulin degludec. Change from baseline in FPG also favored the combination (-46.2 mg/dL versus -12.1 mg/dL).

liraglutide/insulin degludec (Xultophy) versus insulin degludec (Tresiba®)

A phase 3, double-blind trial (NCT01392573) compared liraglutide/insulin degludec and insulin degludec as add-on to metformin (n=398). Basal insulin, sulfonylureas, and glinides were discontinued at randomization. Each study drug was started at a dose of 16 units and the maximum dose was 50 units.[338] Dosages for the combination product and the basal-insulin comparators were titrated based on FPG of < 90 mg/dL. Baseline HbA1c was 8.7% for the combination group and 8.8% for the insulin degludec group. At week 26, change in HbA1c was -1.94% for the combination group and -1.05% for the insulin degludec group; the difference was statistically significant. Percentage of patients that achieved HbA1c < 7% was 57.3% in the combination group and 22.6% in the insulin degludec group. In addition, mean FPG at study end was lower with the combination product than insulin degludec (110 versus 118 mg/dL). The final dose of insulin in each group was 46 units; this study was designed to show the benefit of liraglutide component on glycemic lowering.

liraglutide/insulin degludec (Xultophy) versus insulin glargine U-100 (Lantus)

DUAL 5 (NCT01952145):[339] A phase 3, open-label trial compared liraglutide/insulin degludec with insulin glargine U-100, both given once daily as add-on to metformin, in patients (n=557) inadequately controlled on insulin glargine U-100 and metformin. Starting doses were 16 units and 32 units for the combination and insulin glargine, respectively. Baseline HbA1c were 8.4% in the combination group and 8.2% in the insulin glargine group. Dosages for the combination product and the basal-insulin comparators were titrated based on FPG of 72 to 90 mg/dL. At 26 weeks, average dose for the combination was 41 units and for insulin, glargine was 66 units. HbA1c changed by -1.67% for the combination and -1.16% for insulin glargine. Percentage of patients that achieved HbA1c < 7% was 68.3% in the combination group compared to 46.2% in the insulin glargine group. Mean change in FPG was similar between groups. Treatment with liraglutide/insulin degludec was also associated with

weight loss compared with weight gain with insulin glargine (-1.4 kg for degludec/liraglutide versus 1.8 kg for glargine).

A 26-week, randomized, open-label trial (NCT02773368) compared daily doses of liraglutide/insulin degludec and insulin glargine U-100 in 420 patients with T2DM inadequately controlled on an SGLT2 inhibitor with or without other oral antidiabetic agents (e.g., metformin, pioglitazone, DPP-4 inhibitor); after randomization, the DPP-4 inhibitor was discontinued.[340] The starting dose was 10 units in each group. At week 26, the least square mean change in HbA1c was -1.97% with liraglutide/insulin degludec and -1.59% with insulin glargine. The least square mean change in FPG was -63.8 and -59.9, respectively, while 49% and 41.9% of patients achieved target FPG goal, respectively.

liraglutide/insulin degludec (Xultophy) versus liraglutide (Victoza)

A phase-3, open-label study (NCT01676116) that randomized patients (n=348) who were inadequately controlled on liraglutide and metformin alone or in combination with pioglitazone, sulfonylurea, or both.[341] Oral antidiabetic drugs (OADs) were continued at pre-trial doses. Patients received liraglutide/insulin degludec (starting dose of 16 units) or liraglutide (median dose was 1.7 mg). Dosages for the combination product and the basal-insulin comparators were titrated based on FPG of 72 to 90 mg/dL. Baseline HbA1c was 7.8% in each group. The dose of the combination product was 44 units at trial end. At 26-weeks, change in HbA1c was -1.31% in the combination group compared to -0.36% in the liraglutide group. Percent of patients that achieved HbA1c < 7% was 74.6% and 30.2%, respectively. At study end, mean FPG was lower with the combination than with liraglutide (112 versus 153 mg/dL).

liraglutide/insulin degludec (Xultophy) versus liraglutide (Victoza) versus insulin degludec (Tresiba)

A 26-week, open-label trial (NCT01336023) compared the efficacy and safety of liraglutide/insulin degludec with insulin degludec and with liraglutide in 1,660 patients with inadequately controlled T2DM on 1 or 2 metformin with or without pioglitazone.[342] Once-daily dosing of the study treatment was added to metformin ± pioglitazone in each arm. Starting doses were as follows: liraglutide/insulin degludec 10 units (10 units insulin degludec/0.36 mg liraglutide), insulin degludec 10 units, and liraglutide 0.6 mg with weekly dose increases by 0.6 mg up to 1.8 mg. At 26 weeks, lease square mean change in HbA1c from baseline was 1.81% for the combination, -1.35% with insulin degludec, and -1.21% with liraglutide. The proportion of patients achieving HbA1c < 7% in each arm was 74.1%, 60.5%, and 56%, respectively. Mean change in FPB was -61.8 mg/dL, -59.2 mg/dL, and -32.4 mg/dL, respectively.

lixisenatide (Adlyxin) versus exenatide (Byetta)

The GetGoal-X trial was a randomized, open-label, parallel-group, multicenter, noninferiority study assessing the HbA1c change with lixisenatide once daily versus exenatide twice daily in a total of 634 adults with T2DM inadequately controlled with metformin.[343] Patients were randomized to receive either lixisenatide 20 mcg once daily (n=318) or exenatide 10 mcg twice daily (n=316) for 24-weeks. Lixisenatide achieved the primary efficacy objective of noninferiority to exenatide in terms of HbA1c reduction from baseline to week 24. The least squares (LS) mean change difference between the 2 groups was 0.17% (95% CI, 0.033 to 0.297), meeting a predefined noninferiority margin of 0.4%. Lixisenatide and exenatide provided comparable reductions in FPG (LS mean change difference between the 2 groups was 0.23 mmol/L [4.14 mg/dL; 95% CI, 20.052 - 0.522]). Furthermore, body weight was decreased from baseline for patients receiving each agent (LS mean change difference

between the 2 groups was 1.02 kg [95%CI, 0.456 – 1.581]). The most common adverse events in both groups were gastrointestinal in nature, which occurred less frequently in the lixisenatide group as compared with the exenatide group (43.1% versus 50.6%, respectively). Symptomatic hypoglycemia also occurred less frequently in the lixisenatide group as compared with the exenatide group (2.5% versus 7.9%, respectively).

lixisenatide (Adlyxin) and cardiovascular outcomes

The ELIXA trial was a randomized, multicenter, double-blind, placebo-controlled trial designed to assess the effects of lixisenatide on CV morbidity and mortality.[344] The trial included 6,068 patients with T2DM who experienced an acute coronary event within the last 180 days before screening. Patients were excluded who were < 30 years of age, had a percutaneous intervention within the previous 15 days, a coronary-artery bypass graft surgery for the qualifying event, planned coronary revascularization procedure within 90 days after screening, eGFR < 30 mL/min/1.73m^2, a HbA1c < 5.5% or > 11%, or an inability to provide written informed consent. Eligible patients were randomized to a once-daily SC injection of lixisenatide (starting at 10 mcg daily and increased to 20 mcg daily after the first 2 weeks, at the discretion of the investigators) or placebo. The primary endpoint in the time-to-event analysis was a composite of the first occurrence of any of the following: death from CV causes, nonfatal MI, non-fatal stroke, or hospitalization for unstable angina. The primary endpoint occurred in 406 patients (13.4%) in the lixisenatide group and in 399 (13.2%) in the placebo group (HR 1.02, 95% CI, 0.89 to 1.17); the upper boundary of the 95% CI excluded 1.3 but not 1.0, which showed the noninferiority of lixisenatide to placebo (p<0.001) but not superiority (p=0.81).

lixisenatide/insulin glargine (Soliqua) versus insulin glargine (Lantus)

A randomized, 30-week, active-controlled, open-label, 2-treatment arm, parallel-group study (NCT02058160) enrolled 736 patients with T2DM who had been treated with stable doses of basal insulin (15 to 40 units) for at least 6 months, with or without oral antidiabetic drugs (OADs).[345,346] At screening HbA1c was between 7.5% and 10%. Patients were switched to or remained on insulin glargine U-100 during a 6-week run-in period. At the end of the run-in period, patients with an HbA1c between 7% and 10%, FPG ≤ 140 mg/dL, and insulin glargine daily dose of 20 to 50 units, were randomized to either combination insulin glargine/lixisenatide or insulin glargine U-100. Dosage was titrated to achieve a fasting plasma glucose (FPG) < 100 mg/dL. Maximum insulin glargine dose allowed in either group was 60 units. Target FPG was achieved in 33% of patients in both groups at 30 weeks. At 30 weeks, there was a statistically greater change in HbA1c from baseline for the combination product compared to insulin glargine (mean difference -0.5 [95% confidence interval -0.63, -0.4]). The trial was designed to show the contribution of the GLP-1 component to glycemic lowering and the dosing algorithm was selected to isolate the effect of the GLP-1 component. At week 30, the doses of insulin glargine were the same in both groups (mean 46.7 units). More patients on the combination product achieved HbA1c < 7% (55%) compared with 30% on insulin glargine. Mean body weight decreased by 0.7 kg with the combination and increased by 0.7 kg with insulin glargine (p<0.0001). The incidence of documented symptomatic hypoglycemia (≤ 70 mg/dL) was similar in both groups. Mild gastrointestinal adverse effects were very low but more frequent with the combination product.

lixisenatide/insulin glargine (Soliqua) versus insulin glargine (Lantus) versus lixisenatide (Adlyxin)

Efficacy and safety of combination insulin glargine/lixisenatide were compared to the individual components in 1,170 patients with T2DM inadequately controlled on metformin, with or without a second oral antidiabetic agent (NCT05058147).[347] After a 4-week run-in to optimize metformin and stop other oral antidiabetic drugs, patients were randomized to open-label once-daily insulin glargine/lixisenatide, insulin glargine, or lixisenatide. Doses in both insulin-containing groups were titrated based on FPG <100 mg/dL to a maximum of 60 units/day. The lixisenatide group received a maximum of 20 mcg once daily. At 30 weeks, greater reductions in HbA1c from baseline were reported with the combination compared with either component alone (-1.6%, -1.3%, -0.9%, respectively). More patients achieved HbA1c <7% with the combination (74%) versus insulin glargine (59%) or lixisenatide (33%) (p<0.0001 for all). Mean change in body weight with the combination was -0.3 kg, lixisenatide -2.3 kg, and insulin glargine +1.1 kg, differences were significant. The incidence of symptomatic hypoglycemia (≤70 mg/dL) was similar with the combination and insulin glargine groups (1.4 and 1.2 events/patient-year, respectively) and lower for the lixisenatide group (0.3 events/patient-year). In addition, the combination improved postprandial glycemic control compared to insulin glargine.

semaglutide (Ozempic) versus placebo

SUSTAIN 1:[348] A multinational, 30-week, double-blind clinical trial compared the efficacy of semaglutide to placebo in 388 treatment-naive adults with T2DM treated with diet and exercise alone for ≥ 30 days before screening and a baseline HbA1c of 7% to 10%. Patients were randomized 2:2:1:1 to once-weekly SC semaglutide 0.5 mg or 1 mg or volume-matched placebo for 30 weeks via prefilled pen-injectors. At baseline, the mean HbA1c was 8.05% (standard deviation [SD], 0.85). At week 30, HbA1c significantly decreased in both semaglutide treatment groups compared to placebo (0.5 mg: treatment difference, -1.43% [95% CI, -1.71 to -1.15; p<0.0001]; 1 mg: treatment difference, -1.53% [95% CI, -1.81 to -1.25; p<0.0001]). A statistically significant difference was not found from baseline with placebo. A statistically significant decrease was also found in body weight with both strengths of semaglutide but not with placebo.

semaglutide (Ozempic) versus sitagliptin (Januvia) as add-on to metformin, thiazolidinedione, or both

SUSTAIN 2:[349] A multinational, 56-week, double-blind, active-control, double-dummy, parallel-group clinical trial compared the efficacy of semaglutide to sitagliptin in 1,231 patients with insufficient glycemic control (HbA1c, 7% to 10.5%) despite stable treatment with metformin, thiazolidinediones, or both. Patients were randomized 2:2:1:1 to added once-weekly SC semaglutide 0.5 mg or 1 mg with dummy oral sitagliptin or oral sitagliptin 100 mg/day with dummy SC semaglutide 0.5 mg or 1 mg (active sitagliptin groups were pooled in the analyses). At baseline, the mean HbA1c was 8.1% (SD, 0.93). At week 56, HbA1c was reduced by 1.3% in the semaglutide 0.5 mg group, 1.6% in the semaglutide 1 mg group, and 0.5% with sitagliptin (semaglutide 0.5 mg: treatment difference versus sitagliptin, -0.77% [95% CI, -0.92 to -0.62]; semaglutide 1 mg: treatment difference versus sitagliptin, -1.06% [95% CI, -1.21 to -0.91]; p<0.0001 for noninferiority and superiority for both). A statistically significant decrease was also found in body weight with both strengths of semaglutide compared to sitagliptin.

semaglutide (Ozempic) versus exenatide ER (Bydureon) as add-on to metformin and/or thiazolidinedione and sulfonylureas

SUSTAIN 3:[350] A multinational, randomized, 56-week, open-label clinical trial compared the efficacy of semaglutide to exenatide ER (Bydureon) in 813 patients with insufficient glycemic control (HbA1c, 7% to 10.5%) despite stable treatment with metformin and/or thiazolidinedione and sulfonylureas. Patients were randomized 1:1 to added once-weekly SC semaglutide 1 mg or exenatide ER 2 mg. At baseline, the mean HbA1c was 8.3%. Most patients were on background metformin alone (49%) or metformin plus a sulfonylurea (45%). At week 56, HbA1c was reduced by 1.5% in the semaglutide 1 mg group and 0.9% with exenatide ER (treatment difference versus exenatide ER, -0.62% [95% CI, -0.8 to -0.44; p<0.0001 for noninferiority and superiority]). A statistically greater decrease in body weight was also found with semaglutide compared to exenatide ER.

semaglutide (Ozempic) versus insulin glargine (Lantus) as add-on to metformin alone or in combination with a sulfonylurea

SUSTAIN 4:[351] A multinational, randomized, open-label, noninferiority, parallel-group, 30-week clinical trial compared the efficacy of semaglutide to insulin glargine in 1,089 patients with insufficient glycemic control (HbA1c, 7% to 10%) despite stable treatment with metformin alone or in combination with a sulfonylurea. Patients were randomized 1:1:1 to added once-weekly SC semaglutide 0.5 mg or 1 mg or once-daily insulin glargine (titrated to pre-breakfast plasma glucose of 72 to 99 mg/dL). At baseline, the mean HbA1c was 8.17%. At week 30, the 0.5 mg and 1 mg semaglutide treatment groups had reductions of 1.21% (95% CI, 1.1 to 1.31) and 1.64% (95% CI, 1.54 to 1.74), respectively. The insulin glargine group had a reduction of 0.83% (95% CI, 0.73 to 0.93; estimated treatment difference of semaglutide 0.5 mg versus insulin glargine, -0.38% [95% CI, -0.52 to -0.24; p<0.0001]; estimated treatment difference of semaglutide 1 mg versus insulin glargine, -0.81% [95% CI, -0.96 to -0.67; p<0.0001]). A weight loss was found in both semaglutide groups compared to weight gain in the insulin glargine group.

semaglutide (Ozempic) versus placebo as add-on to basal insulin, with or without metformin

SUSTAIN 5:[352] A multinational, randomized, 30-week, double-blind, phase 3 clinical trial compared the efficacy of semaglutide to placebo in 397 patients with insufficient glycemic control (HbA1c, 7% to 10%) despite stable treatment with basal insulin, with or without metformin. Patients were randomized 2:2:1:1 to semaglutide 0.5 or 1 mg SC once weekly or placebo (2 dummy strengths). Patients with HbA1c ≤ 8% at screening reduced their insulin dose by 20% to reduce the risk of hypoglycemia, but the dose could be titrated up as needed to a maximum pre-trial dose during weeks 10 through 16. At baseline, the mean HbA1c was 8.3% to 8.4%. At week 30, the 0.5 mg and 1 mg semaglutide treatment groups had reductions of 1.3% and 1.7%, respectively. The placebo group had a reduction of 0.2% (estimated treatment difference of semaglutide 0.5 mg versus placebo, -1.1% [95% CI, -1.4 to -0.8; p<0.0001]; estimated treatment difference of semaglutide 1 mg versus placebo, -1.6% [95% CI, -1.8 to -1.3; p<0.0001]). A weight loss was found in both semaglutide groups compared to weight gain in the insulin glargine group.

semaglutide (Ozempic) and cardiovascular outcomes

SUSTAIN 6 (NCT01720446):[353] A multinational, double-blind, 104-week trial compared CV outcomes in 3,297 patients with inadequately controlled T2DM and ASCVD randomized to once-weekly semaglutide

0.5 mg or 1 mg or placebo for 104 weeks, in addition to continuing a standard-care regimen. The primary outcome was a composite of first occurrence of CV death, nonfatal MI, or nonfatal stroke. At baseline, 58.8% of the patients had a history of CVD without chronic kidney disease (CKD), 10.7% had chronic kidney disease only, 13.4% had both, and 17% were at high risk of CV disease. Study analysis prespecified that reporting of results for both doses of the semaglutide would be combined. The primary outcome occurred in 6.6% (108/1,648) and 8.9% (146/1,649) of patients assigned semaglutide and placebo, respectively (HR, 0.74; 95% CI, 0.58 to 0.95; p<0.001 for noninferiority). In regard to individual components of the primary outcome, nonfatal MI occurred in 2.9% and 3.9% of those receiving semaglutide and placebo, respectively (HR, 0.74; 95% CI, 0.51 to 1.08; p=0.12), and nonfatal stroke occurred in 1.6% and 2.7% of those receiving semaglutide and placebo, respectively (HR, 0.61; 95% CI, 0.38 to 0.99; p=0.04). The incidence of death due to CV causes was similar between the two groups (2.7% versus 2.8% in the semaglutide group and placebo group, respectively [HR, 0.98; 95% CI, 0.65 to 1.48; p=0.92]). Notably, new or worsening nephropathy rates were lower in the semaglutide group, but retinopathy complications were significantly higher with the semaglutide group.

semaglutide (Ozempic) versus dulaglutide (Trulicity)

SUSTAIN 7:[354] A 40-week, open-label trial compared semaglutide 0.5 mg with dulaglutide 0.75 mg and semaglutide 1 mg with dulaglutide 1.5 mg. A total of 1,199 patients with T2DM were randomized in a 1:1:1:1 fashion. Reductions in HbA1c for semaglutide 0.5 mg and dulaglutide 0.75 mg were 1.5% and 1.1%, respectively, and 1.8% and 1.4% for semaglutide 1mg and dulaglutide 1.5 mg, respectively. Differences were statistically significant comparing the low doses and high doses. A significantly greater proportion of patients treated with semaglutide versus dulaglutide, at both low and high dosages, achieved HbA1c < 7% (68% and 79% on 0.5 mg and 1 mg semaglutide, respectively, versus 52% and 67% on 0.75 mg and 1.5 mg dulaglutide, respectively). In addition, a greater weight loss was reported with semaglutide treated with (4.6 kg and 6.5 kg on 0.5 mg and 1 mg semaglutide, respectively, versus 2.3 kg and 3 kg on 0.75 mg and 1.5 mg dulaglutide, respectively). The most commonly reported adverse effects were gastrointestinal in nature, and incidences were similar among the groups.

semaglutide (Ozempic) versus liraglutide (Victoza)

A 26-week, double-blind trial compared semaglutide and liraglutide in 705 patients with T2DM who were not controlled with diet and exercise, with or without metformin (HbA1c 7% to 10%).[355,356] Patients were randomized 2:2:1 to semaglutide, liraglutide, or placebo in 1 of 4 volume-matched doses (semaglutide 0.05 mg, 0.1 mg, 0.2 mg, or 0.3 mg and liraglutide 0.3 mg, 0.6 mg, 1.2 mg, or 1.8 mg, with both compared within each volume-matched dose group). Notably, the FDA-approved doses are semaglutide 0.25 mg or 0.5 mg and liraglutide 0.6 mg initially with the dose increasing to 1.2 mg or 1.8 mg. Change in HbA1c with semaglutide ranged from was -1% (0.05 mg) to -2% (0.3 mg) and with liraglutide from -0.5% (0.3 mg) to -1.3% (1.8 mg) (all p<0.001 in favor of volume-matched semaglutide dose). Changes in fasting plasma glucose, and reductions in body weight favored semaglutide over liraglutide. Gastrointestinal adverse effects were reported more often with semaglutide than with liraglutide.

semaglutide (Ozempic) versus canagliflozin (Invokana®)

SUSTAIN 8: This double-blind, parallel-group study compared the efficacy and safety of injectable semaglutide with the SGLT2 inhibitor canagliflozin in adults with uncontrolled T2DM (HbA1c ≥ 7% to ≤ 10.5%) who were on stable metformin therapy.[357] Patients (n=788) were randomized 1:1 to injectable semaglutide 1 mg once weekly or oral canagliflozin 300 mg once daily. At 52 weeks, the estimated difference in change in HbA1c for semaglutide compared to canagliflozin was -0.49% (95% CI, -0.65 to -0.33; p<0.0001). Greater reductions in body weight were reported with semaglutide (estimated difference compared to canagliflozin was -1.06 kg [95% CI, -1.76 to -0.36; p=0.0029]). The most common adverse effect reported with semaglutide was nausea (47%), while infection was most prevalent with canagliflozin (urinary tract infection, 35%). The rate of discontinuation of therapy due to adverse events was 10% with semaglutide and 5% with canagliflozin.

semaglutide (Rybelsus) monotherapy versus placebo

PIONEER 1 (NCT02906930): This 26-week, double-blind trial randomized adults with inadequately controlled T2DM on diet and exercise to monotherapy with daily oral doses of semaglutide 7 mg (n=175), semaglutide 14 mg (n=175), or placebo (n=178).358 The difference in change in HbA1c from baseline was significantly greater for both doses of semaglutide compared to placebo (difference with semaglutide 7 mg, -0.9% [95% CI, -1.1 to -0.6; p<0.001]; difference with semaglutide 14 mg, -1.1% [95% CI, -1.3 to -0.9; p<0.001]). The change in FPG from baseline was -28 mg/dL, -33 mg/dL, and -3 mg/dL for semaglutide 7 mg, semaglutide 14 mg, and placebo, respectively. The proportion of patients who achieved an HbA1c < 7% was significantly greater with semaglutide (69% with 7 mg, and 77% with 14 mg versus 31% with placebo). The mean changes from baseline to week 26 for body weight with semaglutide 7 mg, semaglutide 14 mg, and placebo were -2.3 kg, -3.7 kg, and -1.4 kg, respectively.

semaglutide (Rybelsus) versus empagliflozin as add-on to metformin

PIONEER 2 (NCT02863328): This 26-week, open-label trial randomized adults with T2DM on stable doses of metformin (≥ 1,500 mg/day) to once daily oral doses of semaglutide 14 mg (n=411) or empagliflozin 25 mg (n=410).[359,360] The difference in change in HbA1c from baseline was significantly greater with semaglutide compared to empagliflozin (difference, -0.4%; 95% CI, -0.6 to -0.3; p<0.001). The change in FPG from baseline was the same for both products (-36 mg/dL). The proportion of patients who achieved an HbA1c < 7% was significantly greater with semaglutide than with empagliflozin (67% versus 40%, respectively). The mean changes from baseline to week 26 for body weight with semaglutide and empagliflozin were -3.8 kg and -3.7 kg, respectively.

semaglutide (Rybelsus) versus sitagliptin (Januvia)

PIONEER 3 (NCT02607865): This 26-week, double-blind trial randomized adults with T2DM on metformin with or without sulfonylurea to once daily oral doses of semaglutide 7 mg (n=465), semaglutide 14 mg (n=465), or sitagliptin 100 mg (n=467).[361,362] The difference in change in HbA1c from baseline was significantly greater with both doses of semaglutide compared to sitagliptin (difference with semaglutide 7 mg, -0.3% [95% CI, -0.4 to -0.1]; difference with semaglutide 14 mg, -0.5% [95% CI, -0.6 to -0.4]; p<0.001 for both). The change in FPG from baseline was -21 mg/dL, -31 mg/dL, and -15 mg/dL for semaglutide 7 mg, semaglutide 14 mg, and sitagliptin, respectively. The proportion of patients who achieved an HbA1c < 7% was 44% with semaglutide 7 mg, 56% with semaglutide 14 mg, and 32% with sitagliptin. The mean changes from baseline to week 26 for body

weight with semaglutide 7 mg, semaglutide 14 mg, and sitagliptin were -2.2 kg, -3.1 kg, and -0.6 kg, respectively.

PIONEER 7 (NCT02849080): This 52-week, open-label trial randomized patients with inadequately controlled T2DM (HbA1c of 7.5% to 9.5%) with 1 or 2 stable antidiabetic medications.[363] Patients were assigned to oral semaglutide (n=253) with flexible dosed (adjusted based on prespecified criteria) to 7 mg or 14 mg once daily or sitagliptin 100 mg (n=251) once daily. At 52 weeks, a statistically greater proportion of patients treated with semaglutide achieved an HbA1c of < 7% compared to sitagliptin (58% versus 25%, respectively). The confirmatory secondary efficacy endpoint was bodyweight from baseline to week 52, which was -2.6 kg with semaglutide and -0.7 with sitagliptin.

semaglutide (Rybelsus) versus liraglutide (Victoza)

PIONEER 4 (NCT02863419): This 26-week, double-blind trial randomized adults with T2DM on metformin with or without an SGLT2 inhibitor to semaglutide 14 mg orally once daily (n=285), liraglutide 1.8 SC once daily (n=284), or placebo (n=142).[364,365] While the difference in change in HbA1c from baseline for semaglutide compared to placebo was significantly significant (-1.1%; 95% CI, -1.2 to -0.9; p<0.001) the difference compared to liraglutide was not significantly significant (-0.1%; 95% CI, -0.3 to 0). The change in FPG from baseline was -36 mg/dL, -34 mg/dL, and -7 mg/dL for semaglutide, liraglutide, and placebo, respectively. The proportion of patients who achieved an HbA1c < 7% was 68% with semaglutide, 62% with liraglutide, and 14% with placebo. The mean changes from baseline to week 26 for body weight with semaglutide, liraglutide, and placebo were -4.4 kg, -3.1 kg, and -0.5 kg, respectively.

semaglutide (Rybelsus) versus placebo in patients with renal impairment

PIONEER 5 (NCT02827708): Semaglutide demonstrated efficacy in adults with moderate renal impairment. This 26-week, double-blind trial randomized patients with T2DM and moderate renal impairment to semaglutide 14 mg or placebo orally once daily as add-on to their stable background antidiabetic regimen (including metformin and/or sulfonylurea and/or basal insulin). The semaglutide dose was reduced by 20% in patients on basal insulin.[366,367] The difference in change in HbA1c from baseline was significantly greater with semaglutide compared to placebo (difference, -0.8%; 95% CI, -1 to -0.6; p<0.001). The change in FPG from baseline was -28 mg/dL and -7 mg/dL for semaglutide and placebo, respectively. The proportion of patients who achieved an HbA1c < 7% was 58% and 23% with semaglutide and placebo, respectively. The mean changes from baseline to week 26 for body weight with semaglutide and placebo were -3.4 mg, and -0.9 kg, respectively.

semaglutide (Rybelsus) versus insulin

PIONEER 8 (NCT03021187): This 26-week, double-blind trial randomized adults with inadequately controlled T2DM insulin (basal, basal/bolus, or premixed) with or without metformin to with daily oral doses of semaglutide 7 mg (n=182), semaglutide 14 mg (n=181), or placebo (n=184).[368,369] The insulin dose was decreased by 20% at randomization to lessen the risk of hypoglycemia. The difference in change in HbA1c from baseline was significantly greater for both doses of semaglutide compared to placebo (difference with semaglutide 7 mg, -0.9% [95% CI, -1.1 to -0.7]; difference with semaglutide 14 mg, -1.2% [95% CI, -1.4 to -1]; p<0.001 for both). The change in FPG from baseline was -20 mg/dL, -24 mg/dL, and +5 mg/dL for semaglutide 7 mg, semaglutide 14 mg, and placebo, respectively. The proportion of patients who achieved an HbA1c < 7% was significantly greater with semaglutide (43%

with 7 mg and 58% with 14 mg versus 7% with placebo). The mean changes from baseline to week 26 for body weight with semaglutide 7 mg, semaglutide 14 mg, and placebo were -2.4 kg, -3.7 kg, and -0.4 kg, respectively.

semaglutide (Rybelsus) and cardiovascular outcomes

PIONEER 6 (NCT02692716): A double-blind , placebo-controlled trial randomized 3,183 patients ≥ 50 years of age with inadequately controlled T2DM and ASCVD to oral semaglutide 14 mg once daily or placebo, as add-on to standard of care.[370,371] The study included patients with CKD. Median follow up was 16 months. The primary endpoint was the time to first occurrence of MACE (composite of CV death, non-fatal myocardial infarction and non-fatal stroke). The proportion of patients who experienced ≥ 1 MACE was 3.8% with semaglutide and 4.8% with placebo. Noninferiority of semaglutide to placebo was demonstrated (HR, 0.79; 95% CI, 0.57 to 1.11).

META-ANALYSES

A meta-analysis of all the published and unpublished studies (n=21) evaluated the efficacy and safety of the GLP-1 receptor agonists, exenatide and liraglutide.[372] Studies were at least 12 weeks in duration and analyzed for HbA1c, body weight changes, and hypoglycemia and other adverse events. A total of 8,482 patients with T2DM received a GLP-1 agonist (n=5,429) or either placebo or an active comparator (n=3,053). A significant improvement in HbA1c over placebo was observed (-1, 95% CI, -1.1 to -0.8; p<0.001). Low rates of hypoglycemia were observed. Gastrointestinal adverse effects are reported frequently; however, weight loss is reported. No evidence of increased CV risk with the use of GLP-1 receptor agonists was found. GLP-1 receptor agonists result in both weight loss and gastrointestinal adverse effects. GLP-1 receptor agonists effectively reduce HbA1C and postprandial glucose. According to the meta-analysis in patients failing sulfonylurea and/or metformin, GLP-1 receptor agonists have similar efficacy as insulin. Furthermore, liraglutide was found to be comparable to exenatide.

A network meta-analysis and systematic review included 34 randomized, controlled trials (n=21,126) of at least 24 weeks in duration and compared the efficacy and safety of once-weekly GLP-1 receptor agonists in adults with T2DM.[373] Data sources were electronic databases (PubMed, Web of Science, Cochrane Central Register of Controlled Trials, FDA, European Medicines Agency, ClinicalTrials.gov) and congress abstracts from inception through 26 September 2015. Drugs in the study included albiglutide (now discontinued/no longer available), dulaglutide, once-weekly exenatide, or taspoglutide (taspoglutide is not currently approved in the US). Compared to placebo, the mean reduction in HbA1c were the following: dulaglutide 1.5 mg -1.4% (95% CI, -1.6 to -1.2); once-weekly exenatide -1.3% (95% CI, -1.5 to -1.1); dulaglutide 0.75 mg -1.2% (95% CI, -1.4 to -1); taspoglutide 20 mg -1.1% (95% CI, -1.3 to -0.9); and taspoglutide 10 mg -0.9% (95% CI, -1.2 to -0.8). When once-weekly GLP-1RAs were compared, exenatide was associated with a greater fasting plasma glucose reduction versus dulaglutide 0.75 mg and taspoglutide, 10 mg, and were FPG reductions were similar to taspoglutide 20 mg, and dulaglutide 1.5 mg. Risk for hypoglycemia among once-weekly GLP-1 receptor agonists was similar. In addition, once-weekly exenatide increased heart rate compared with dulaglutide (1.4 to 3.2 beats/min); taspoglutide 20 mg was associated with the greatest risk for nausea.

Another meta-analysis was conducted of published randomized clinical trials of 24 to 32 weeks in duration that compared a GLP-1 agonist (albiglutide [now discontinued/no longer available],

dulaglutide, twice-daily exenatide, once-weekly exenatide, liraglutide, lixisenatide, semaglutide and taspoglutide) with placebo or another GLP-1 agonist and were published through June 3, 2016.[374] A total of 34 studies were identified (n=14,464). Dulaglutide, liraglutide, and once-weekly exenatide were superior to twice-daily exenatide and lixisenatide at lowering HbA1c and FPG levels. There were no differences in hypoglycemia between these 3 agents. No data were reported for semaglutide. Taspoglutide is not available in the US.

A meta-analysis including 43 randomized (n=19,101) controlled trials lasting at least 12 weeks involving DPP-4 inhibitors was conducted.[375] Of participants evaluated for the primary endpoint, 10,467 were treated with a DPP-4 inhibitor and 8,634 treated with placebo or a comparator drug. DPP-4 inhibitors showed a statistically significant reduction in HbA1c compared to placebo and approximately 40% of participants achieved the HbA1c goal of < 7%, which was associated with weight neutrality and no greater hypoglycemia. Baseline HbA1c was the best predictor for achievement of HbA1C target ($p<0.001$).

According to a meta-analysis which included 10 randomized trials and over 6,500 patients, the addition of a DPP-4 inhibitor to a sulfonylurea in patients with T2DM increases the risk for hypoglycemia compared to sulfonylureas alone.[376] Results indicate the need to follow existing recommendations to reduce the dose of sulfonylureas when used in combination with DPP-4 inhibitors.

A systemic review of 32 clinical trials published through 2015 that included a total of 13,747 patients with T2DM found no significant difference in efficacy between linagliptin and sitagliptin.[377] Single-component or combination products with metformin were compared to placebo in the studies.

A meta-analysis including 8 trials (n=21,135) evaluated the effect of GLP-1 receptor agonists (liraglutide, lixisenatide, semaglutide, and albiglutide [now discontinued]) on CV outcomes and all-cause mortality compared to placebo in patients with or at high risk of CVD.[378] The risk of all-cause mortality was 11% lower (RR, 0.89; 95% CI, 0.81 to 0.99) with GLP-1 receptor agonists compared to placebo; no difference between the groups regarding CV death, nonfatal MI, nonfatal stroke, or heart failure hospitalizations was found. Likewise, another meta-analysis with 4 placebo-controlled studies including liraglutide, lixisenatide, semaglutide, and exenatide ER reported a 12% reduction in all-cause mortality (RR, 0.88; 95% CI, 0.81 to 0.95; p=0.002), a 10% relative risk reduction in composite CV death, non-fatal MI, and non-fatal stroke, and a 13% relative risk reduction in CV mortality (HR 0.87; 95% CI, 0.79 to 0.96); no significant impact on MI, stoke, or hospitalization for unstable angina or heart failure were reported.[379]

SUMMARY

Subcutaneous pramlintide (Symlin), for the management of types 1 and 2 diabetes, is indicated to be co-administered with mealtime insulin and, in this setting, there is an increased risk of severe hypoglycemia. For pramlintide, HbA1c improvements are 0.3% to 0.6% with a potential weight reduction of 0.5 kg to 1.5 kg. Pramlintide should not be used in patients with confirmed gastroparesis.

The dipeptidyl peptidase-4 (DPP-4) inhibitors, indicated for adult patients with type 2 diabetes (T2DM), have modest glucose-lowering effects with HbA1c decrements of 0.5% to 1%. These agents are weight-neutral and have a low hypoglycemia risk when used as monotherapy or in conjunction with metformin. Once-daily fixed-dose combinations of a DPP-4 inhibitor and a sodium-dependent glucose cotransporter 2 (SGLT2) inhibitor, including linagliptin/empagliflozin (Glyxambi),

saxagliptin/dapagliflozin (Qtern), and sitagliptin/ertugliflozin (Steglujan), are also available and are associated with a reduction in body weight compared to linagliptin or saxagliptin alone. Concerns regarding the increased risk of pancreatitis and pancreatic cancer remain unresolved, although recent data have indicated a lack of an association between DPP-4 inhibitors and pancreatic adverse effects. DPP-4 inhibitors are administered orally and are dosed once daily, except those that are available in combination with immediate-release metformin (alogliptin/metformin [Kazano], linagliptin/metformin [Jentadueto], and sitagliptin/metformin [Janumet]). Combination products of DDP-4 inhibitors are also available in combination with extended-release metformin and are taken once daily. They include linagliptin/metformin ER (Jentadueto XR), saxagliptin/metformin ER (Kombiglyze XR), and sitagliptin/metformin ER (Janumet XR). In addition, fixed-dose triple combination therapy with a DPP-4 inhibitor, an SGLT2 inhibitor, and extended-release metformin are available as linagliptin/empagliflozin/metformin ER (Trijardy XR) and saxagliptin/dapagliflozin/metformin ER (Qternmet XR).

The glucagon-like peptide-1 (GLP-1) receptor agonists dulaglutide (Trulicity), exenatide (Byetta, Bydureon, Bydureon BCise), liraglutide (Victoza), lixisenatide (Adlyxin), and semaglutide (Ozempic, Rybelsus) are indicated for patients with T2DM. All GLP-1 receptor agonists are administered by subcutaneous injection, with the exception of semaglutide tablets (Rybelsus) which marks the first orally administered agent in this class. Based on clinical trials, dulaglutide with a reduction of 0.7% to 1.6%, exenatide and liraglutide with a reduction in HbA1c of 0.5% to 1.6%, lixisenatide with a reduction of 0.3% to 0.65%, injectable semaglutide with a reduction of 1.4% to 1.5%, and oral semaglutide with a reduction of 1.2% to 1.4%. Many study participants experienced a decrease in weight of 0.4 kg to 3.7 kg from baseline. Risks of GLP-1 agonists include the potential for acute pancreatitis and thyroid C-cell tumors including medullary thyroid carcinoma. Hypoglycemia is not usually associated with GLP-1 agonist therapy unless used in combination with an insulin secretagogue or insulin. GLP-1 agonists are administered by subcutaneous injection; exenatide (Byetta) is dosed twice daily, liraglutide and lixisenatide are dosed once daily, while long-acting dulaglutide, exenatide ER (Bydureon, Bydureon BCise), and semaglutide (Ozempic) are dosed once weekly. Orally administered semaglutide (Rybelsus) is dosed once daily. Combination products offer an additional mechanism to lower blood glucose for patients not meeting HbA1c goals on monotherapy. Liraglutide/insulin degludec (Xultophy) and lixisenatide/insulin glargine (Soliqua) are fixed-dose combinations of a GLP-1 agonist and a long-acting insulin; both products are dosed once-daily.

Use of GLP-1 agonists have not been studied in patients with severe gastrointestinal disease, including severe gastroparesis; therefore, they are not recommended for patients with severe gastrointestinal disease.

As reported by the LEADER trial, liraglutide is associated with a significant 13% relative reduction (RR) in composite cardiovascular (CV) risk (death from CV cause, nonfatal myocardial infarction [MI], or nonfatal stroke). While the rate of death from CV or other causes was lower with liraglutide, the rates of nonfatal MI, nonfatal stroke, and hospitalization for heart failure were not statistically significantly lower than with placebo. The ELIXA, EXSCEL, and TECOS studies reported that lixisenatide (Adlyxin), exenatide ER (Bydureon, Bydureon BCise), and sitagliptin have a neutral effect on CV risk, respectively. The SUSTAIN 6 and PIONEER 6 trials found that subcutaneous and oral formulations of semaglutide were noninferior to placebo in the CV events (composite CV death, nonfatal MI, or nonfatal stroke). A

possible slight increased risk of heart failure with saxagliptin and alogliptin was found in SAVOR-TIMI and EXAMINE trials, respectively.

Although no studies have been published on CV outcomes with linagliptin/empagliflozin (Glyxambi), the EMPA-REG OUTCOME study has been published that evaluated the SGLT2 inhibitor, empagliflozin, which is a component of Glyxambi. The study reported approximately a one-third relative risk reduction for CV death, hospitalization due to heart failure, and all-cause death with use of empagliflozin (Jardiance) as compared to placebo. In addition, the CARMELINA trial demonstrated noninferiority of linagliptin to placebo in CV outcomes.

Clinical trials of alogliptin, saxagliptin and sitagliptin do not show any benefit on major CVD events; however, a modest but significant increased risk of hospitalization for heart failure (HF) was observed with saxagliptin and with alogliptin (only in subjects with no history of HF), but not with sitagliptin.

When lifestyle management and metformin do not adequately control T2DM, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend the addition of a SGLT2 inhibitor or GLP-1 agonist with proven CV or renal benefit in patients with atherosclerotic cardiovascular disease (ASCVD) or chronic kidney disease (CDK), or in patients with clinical heart failure and ASCVD (SGLT2 inhibitor preferred).

REFERENCES

1 Symlin [package insert]. Wilmington, DE; AstraZeneca; December 2019.
2 Nesina [package insert]. Deerfield, IL; Takeda; June 2019.
3 Kazano [package insert]. Deerfield, IL; Takeda; June 2019.
4 Oseni [package insert]. Deerfield, IL; Takeda; June 2019.
5 Tradjenta [package insert]. Ridgefield, CT; Boehringer Ingelheim; July 2019.
6 Glyxambi [package insert]. Ridgefield, CT; Boehringer Ingelheim; January 2020.
7 Trijardy XR [package insert]. Ridgefield CT, Boehringer Ingelheim; January 2020.
8 Jentadueto [package insert]. Ridgefield, CT; Boehringer Ingelheim; July 2019.
9 Jentadueto XR [package insert]. Ridgefield, CT; Boehringer Ingelheim; July 2019.
10 Onglyza [package insert]. Wilmington DE; AstraZeneca; July 2019.
11 Qtern [package insert]. Wilmington DE; AstraZeneca; January 2020.
12 Qternmet XR [package insert]. Wilmington DE; AstraZeneca; January 2020.
13 Kombiglyze XR [package insert]. Wilmington DE; AstraZeneca; October 2019.
14 Januvia [package insert]. Whitehouse Station, NJ; Merck; August 2019.
15 Steglujan [package insert]. Whitehouse Station, NJ; Merck; January 2020.
16 Janumet [package insert]. Whitehouse Station, NJ; Merck; August 2019.
17 Janumet XR [package insert]. Whitehouse Station, NJ; Merck; August 2019.
18 Trulicity [package insert]. Indianapolis, IN; Eli Lilly; January 2019.
19 Byetta [package insert]. Wilmington, DE; AstraZeneca; December 2018.
20 Bydureon [package insert]. Wilmington, DE; AstraZeneca; February 2019.
21 Bydureon BCise [package insert]. Wilmington, DE; AstraZeneca; July 2019.
22 Victoza [package insert]. Princeton, NJ; Novo Nordisk; June 2019.
23 Xultophy [package insert]. Plainsboro, NJ; Novo Nordisk; November 2019.
24 Adlyxin [package insert]. Bridgewater, NJ; Sanofi-Aventis; July 2016.
25 Soliqua [package insert]. Bridgewater, NJ; Sanofi-Aventis; November 2019.
26 Ozempic [package insert]. Plainsboro, NJ; Novo Nordisk; January 2020.
27 Ryblesus [package insert]. Plainsboro, NJ; Novo Nordisk; January 2020.
28 Albiglutide. Current and resolved drug shortages and discontinuations reported to FDA. Available at: https://www.accessdata.fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm?AI=Albiglutide+%28Tanzeum%29+Injection&st=d&tab=tabs-2. Accessed February 26, 2020.
29 American Diabetes Association: Standards of Medical Care in Diabetes-2020. Glycemic Targets. Diabetes Care. 2020; 43 (Suppl 1): S66-S76. DOI: 10.2337/dc20-S006. Available at: https://professional.diabetes.org/content-page/practice-guidelines-resources. Accessed February 26, 2020.
30 American Diabetes Association: Standards of Medical Care in Diabetes-2020. Management of Diabetes in Pregnancy. Diabetes Care. 2020; 43 (Suppl 1): S183-S192. DOI: 10.2337/dc20-S014. Available at: https://professional.diabetes.org/content-page/practice-guidelines-resources. Accessed February 26, 2020.

31 American Diabetes Association: Standards of Medical Care in Diabetes-2020. Pharmacologic Approaches to Glycemic Treatment. Diabetes Care. 2020; 43 (Suppl 1): S98-S110. DOI: 10.2337/dc20-S009. Available at: https://professional.diabetes.org/content-page/practice-guidelines-resources. Accessed February 26, 2020.
32 Garber AJ, Handelsman Y, Grunberger G, et al. AACE/ACE Comprehensive Type 2 Diabetes Management Algorithm - Executive Summary - 2020. Endocr Pract. 2020;26(1): 107-133. DOI: 10.4158/CS-2019-0472. Available at: https://www.aace.com/disease-state-resources/diabetes/clinical-practice-guidelines-treatment-algorithms/comprehensive. Accessed February 26, 2020.
33 AACE/ACE Comprehensive Type 2 Diabetes Management Algorithm – 2020. Available at: https://www.aace.com/disease-state-resources/diabetes/clinical-practice-guidelines-treatment-algorithms/comprehensive. Accessed February 26, 2020.
34 American Association of Clinical Endocrinologists and American College of Endocrinology - Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan - 2015. Available at: http://asap.aace.com/publications/guidelines. February 26, 2020.
35 LeRoith D, Biessels GJ, Braithwaite SS, et al. Treatment of diabetes in older adults guideline resources. The Journal of Clinical Endocrinology & Metabolism 2019; 104 (5):1520–1574. DOI:10.1210/jc.2019-00198. Available at: https://www.endocrine.org/guidelines-and-clinical-practice/clinical-practice-guidelines. Accessed February 26, 2020.
36 Qaseem A, Berry MJ, Humphrey LL, et al. Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline Update from the American College of Physicians - 2017. Ann Intern Med. 2017;166:279-290. DOI: 10.7326/M16-1860. Available at: https://www.acponline.org/clinical-information/guidelines. Accessed on February 26, 2020.
37 Qaseem A, Wilt TJ, Kansagara D, et al. Hemoglobin A1c Targets for Glycemic Control With Pharmacologic Therapy for Nonpregnant Adults With Type 2 Diabetes Mellitus: A Guidance Statement Update From the American College of Physicians - 2018. Ann Intern Med. 2018. DOI: 10.7326/M17-0939. Available at: https://www.acponline.org/clinical-information/guidelines. Accessed February 26, 2020.
38 Davies MJ, D; Alessio DA, Fradkin J, et al. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). DOI: 10.2337/dci18-0033. Available at: https://www.easd.org/statements.html. Accessed February 26, 2020.
39 Guidelines on Second- and Third-line Medicines and Type of Insulin for the Control of Blood Glucose Levels in Non-pregnant Adults with Diabetes Mellitus. Geneva: World Health Organization; 2018. Available at: http://apps.who.int/iris/bitstream/handle/10665/272433/9789241550284-eng.pdf?ua=1. Accessed February 26, 2020.
40 Classification of diabetes mellitus. April 2019. World Health Organization. Available at: https://www.who.int/health-topics/diabetes. Accessed February 26, 2020.
41 Pratley RE. Overview of glucagons-peptide-1 analogs and dipeptidyl peptidase-4 inhibitors for type 2 diabetes. Medscape J Med. 2008; 10(7):171.
42 Symlin [package insert]. Wilmington, DE; AstraZeneca; December 2019.
43 Glyxambi [package insert]. Ridgefield, CT; Boehringer Ingelheim; January 2020.
44 Onglyza [package insert]. Wilmington DE; AstraZeneca; July 2019.
45 Soliqua [package insert]. Bridgewater, NJ; Sanofi-Aventis; November 2019.
46 Xultophy [package insert]. Plainsboro, NJ; Novo Nordisk; November 2019.
47 Qtern [package insert]. Wilmington DE; AstraZeneca; January 2020.
48 Ozempic [package insert]. Plainsboro, NJ; Novo Nordisk; January 2020.
49 Steglujan [package insert]. Whitehouse Station, NJ; Merck; January 2020.
50 Ryblesus [package insert]. Plainsboro, NJ; Novo Nordisk; January 2020.
51 Trijardy XR [package insert]. Ridgefield, CT; Boehringer Ingelheim; January 2020.
52 Symlin [package insert]. Wilmington, DE; AstraZeneca; December 2019.
53 Onglyza [package insert]. Wilmington DE; AstraZeneca; July 2019.
54 Kombiglyze XR [package insert]. Wilmington DE; AstraZeneca; October 2019.
55 Januvia [package insert]. Whitehouse Station, NJ; Merck; August 2019.
56 Qtern [package insert]. Wilmington DE; AstraZeneca; January 2020.
57 Janumet [package insert]. Whitehouse Station, NJ; Merck; August 2019.
58 Tradjenta [package insert]. Ridgefield, CT; Boehringer Ingelheim; July 2019.
59 Trijardy XR [package insert]. Ridgefield, CT; Boehringer Ingelheim; January 2020.
60 Glyxambi [package insert]. Ridgefield, CT; Boehringer Ingelheim; January 2020.
61 Glucophage/Glucophage XR [package insert]. Princeton, NJ; Bristol-Myers Squibb; January 2009.
62 Janumet [package insert]. Whitehouse Station, NJ; Merck; August 2019.
63 Kombiglyze XR [package insert]. Wilmington DE; AstraZeneca; October 2019.
64 Onglyza [package insert]. Wilmington DE; AstraZeneca; July 2019.
65 Tanzeum [package insert]. Wilmington, DE; GlaxoSmithKline; December 2017.
66 Nesina [package insert]. Deerfield, IL; Takeda; June 2019.
67 Trulicity [package insert]. Indianapolis, IN; Eli Lilly; January 2019.
68 Byetta [package insert]. Wilmington, DE; AstraZeneca; December 2018.
69 Bydureon [package insert]. Wilmington, DE; AstraZeneca; February 2019.
70 Bydureon BCise [package insert]. Wilmington, DE; AstraZeneca; July 2019.
71 Gupta V. Glucagon-like peptide-1 analogues: An overview. Indian J Endocrinol Metab. 2013; 17(3): 413–421. DOI: 10.4103/2230-8210.111625.
72 Victoza [package insert]. Princeton, NJ; Novo Nordisk; June 2019.
73 Adlyxin [package insert]. Bridgewater, NJ; Sanofi-Aventis; July 2016.
74 Soliqua [package insert]. Bridgewater, NJ; Sanofi-Aventis; November 2019.
75 Xultophy [package insert]. Plainsboro, NJ; Novo Nordisk; November 2019.
76 Tresiba [package insert]. Plainsboro, NJ; Novo Nordisk; December 2016.
77 Ozempic [package insert]. Plainsboro, NJ; Novo Nordisk; January 2020.

78 Steglujan [package insert]. Whitehouse Station, NJ; Merck; January 2020.
79 Rybelsus [package insert]. Plainsboro, NJ; Novo Nordisk; January 2020.
80 Tibble CA, Cavaiola TS, Henry RR. Longer acting GLP-1 receptor agonists and the potential for improved cardiovascular outcomes. Available at: http://www.medscape.com/viewarticle/803916_4. Accessed February 26, 2020.
81 Jimenez-Solem E1, Rasmussen MH, Christensen M, et al. Dulaglutide, a long-acting GLP-1 analog fused with an Fc antibody fragment for the potential treatment of type 2 diabetes. Curr Opin Mol Ther. 2010;12(6):790-797.
82 Meier JJ, GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. Nature Reviews Endocrinology. 2012; 8: 728-742. DOI: 10.1038/nrendo.2012.140.
83 Nesina [package insert]. Deerfield, IL; Takeda; June 2019.
84 Kazano [package insert]. Deerfield, IL; Takeda; June 2019.
85 Oseni [package insert]. Deerfield, IL; Takeda; June 2019.
86 Byetta [package insert]. Wilmington, DE; AstraZeneca; December 2018.
87 Bydureon [package insert]. Wilmington, DE; AstraZeneca; February 2019.
88 Bydureon BCise [package insert]. Wilmington, DE; AstraZeneca; July 2019.
89 Victoza [package insert]. Princeton, NJ; Novo Nordisk; June 2019.
90 Symlin [package insert]. Wilmington, DE; AstraZeneca; December 2019.
91 Janumet [package insert]. Whitehouse Station, NJ; Merck; August 2019.
92 Janumet XR [package insert]. Whitehouse Station, NJ; Merck; August 2019.
93 Januvia [package insert]. Whitehouse Station, NJ; Merck; August 2019.
94 Onglyza [package insert]. Wilmington DE; AstraZeneca; July 2019.
95 Qtern [package insert]. Wilmington DE; AstraZeneca; January 2020.
96 Qternmet XR [package insert]. Wilmington DE; AstraZeneca; January 2020.
97 Kombiglyze XR [package insert]. Wilmington DE; AstraZeneca; October 2019.
98 Tradjenta [package insert]. Ridgefield, CT; Boehringer Ingelheim; July 2019.
99 Jentadueto [package insert]. Ridgefield, CT; Boehringer Ingelheim; July 2019.
100 Tanzeum [package insert]. Wilmington, DE; GlaxoSmithKline; December 2017.
101 Trulicity [package insert]. Indianapolis, IN; Eli Lilly; January 2019.
102 Glyxambi [package insert]. Ridgefield, CT; Boehringer Ingelheim; January 2020.
103 Trijardy XR [package insert]. Ridgefield, CT; Boehringer Ingelheim; January 2020.
104 Adlyxin [package insert]. Bridgewater, NJ; Sanofi-Aventis; July 2016.
105 Soliqua [package insert]. Bridgewater, NJ; Sanofi-Aventis; November 2019.
106 Xultophy [package insert]. Plainsboro, NJ; Novo Nordisk; November 2019.
107 Ozempic [package insert]. Plainsboro, NJ; Novo Nordisk; January 2020.
108 Steglujan [package insert]. Whitehouse Station, NJ; Merck; January 2020.
109 Ryblesus [package insert]. Plainsboro, NJ; Novo Nordisk; January 2020.
110 Bonora E, Ciqolini M. DPP-4 inhibitors and cardiovascular disease in type 2 diabetes mellitus. Expectations, observations and perspectives. Nutr Metab Cardiovasc Dis. 2016; 26(4):273-84. DOI: 10.1016/j.numecd.2016.03.002.
111 Rosenstock J, Perkovic V, Johansen OD, et al. Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: the CARMELINA randomized clinical trial. JAMA. 2019; 321(1):69-79. DOI: 10.1001/jama.2018.18269.
112 Rosenstock J, Kahn SE, Johansen OE, et al. Effect of linagliptin vs glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes: the CAROLINA randomized clinical trial. JAMA. 2019 Sep 19. DOI: 10.1001/jama.2019.13772.
113 FDA Drug Safety Communication: FDA investigating reports of possible increased risk of pancreatitis and pre-cancerous findings of the pancreas from incretin mimetic drugs for type 2 diabetes. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm343187.htm. Accessed February 26, 2020.
114 Egan AG, Blind E, Dunder K, et al. Pancreatic safety of incretin-based drugs — FDA and EMA Assessment. NEJM. 2014; 370:794-797.
115 Singh S, Chang HY, Richards TM, et al. Glucagonlike peptide 1–based therapies and risk of hospitalization for acute pancreatitis in type 2 diabetes mellitus a population-based matched case-control Study. JAMA Intern Med. 2013; 173(7):534-539. DOI:10.1001/jamainternmed.2013.2720.
116 American Association of Clinical Endocrinologists. Available at: http://www.diabetescare.net/article/title/aace-ada-issue-joint-response-to-published-jama-article-on-glp-1-therapy. Accessed February 26, 2020.
117 Handelsman Y, LeRoith D, Bloomgarden ZT, et al. Diabetes and cancer-an AACE/ACE consensus statement. 2013. Endoc Prac. 2013; 19(4):675-693. Available at: https://www.aace.com/publications/position-statements. Accessed February 26, 2020.
118 Food and Drug Administration. FDA Drug Safety Communication: FDA requires label warnings to prohibit sharing of multi-dose diabetes pen devices among patients. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm435271.htm. Accessed February 26, 2020.
119 White WB, Bakris GL, Bergenstal RM, et al. EXamination of cArdiovascular outcoMes with alogliptIN versus standard of carE in patients with type 2 diabetes mellitus and acute coronary syndrome (EXAMINE): a cardiovascular safety study of the dipeptidyl peptidase 4 inhibitor alogliptin in patients with type 2 diabetes with acute coronary syndrome. Am Heart J. 2011; 162(4):620-626.e1. DOI: 10.1016/j.ahj.2011.08.004.
120 Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. NEJM 2013; 369:1317-1326. DOI: 10.1056/NEJMoa1307684.
121 Food and Drug Administration. Diabetes medications containing saxagliptin and alogliptin: Drug Safety Communication - Risk of heart failure. Available at: https://wayback.archive-it.org/7993/20170404200709/https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm494252.htm. Accessed February 26, 2020.
122 FDA Drug Safety Communication: FDA adds warnings about heart failure risk to labels of type 2 diabetes medicines containing saxagliptin and alogliptin. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm486096.htm. Accessed February 26, 2020.

123 Weir DL, McAlister FA, Senthilselvan A, et al. Sitagliptin use in patients with diabetes and heart failure: A population-based retrospective cohort study. JACC Heart Fail. 2014; S2213-1779(14)00194-2. DOI: 10.1016/j.jchf.2014.04.005.
124 Green JB, Bethel MA, Armstrong PW, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. NEJM. 2015; 16;373(3):232-42. DOI: 10.1056/NEJMoa1501352.
125 Food and Drug Administration. SGLT2 inhibitors: Drug Safety Communication - FDA warns medicines may result in a serious condition of too much acid in the blood. Available at: https://wayback.archive-it.org/7993/20170112164021/http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm446994.htm. Accessed February 26, 2020.
126 Food and Drug Administration. Supplemental approval letter. Janumet XR Available at: http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/20 2270Orig1s006ltr.pdf. Accessed February 26, 2020.
127 Food and Drug Administration. DPP-4 Inhibitors for type 2 diabetes: Drug Safety Communication - May Cause Severe Joint Pain. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm460238.htm. Accessed February 26, 2020.
128 Food and Drug Administration. FDA warns about rare occurrences of a serious infection of the genital area with SGLT2 inhibitors for diabetes. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm617360.htm. Accessed February 26, 2020.
129 Food and Drug Administration. Center for Drug Evaluation and Research. Application number: 125431Orig1s000. Summary review. Tanzeum. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125431Orig1s000SumR.pdf. February 26, 2020.
130 Food and Drug Administration. Center for Drug Evaluation and Research. Application number: 125469Orig1s000. Summary review. Trulicity. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125469Orig1s000SumR.pdf. Accessed February 26, 2020.
131 Food and Drug Administration. Center for Drug Evaluation and Research. Application number: 22-341. Summary Review. Victoza. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000sumr.pdf. Accessed February 26, 2020.
132 Food and Drug Administration. Center for Drug Evaluation and Research. Application number: 125469Orig1s000. Clinical Pharmacology and Biopharmaceutics Review(s). Dulaglutide. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125469Orig1s000ClinPharmR.pdf. Accessed February 26, 2020.
133 Nesina [package insert]. Deerfield, IL; Takeda; June 2019.
134 Kazano [package insert]. Deerfield, IL; Takeda; June 2019.
135 Oseni [package insert]. Deerfield, IL; Takeda; June 2019.
136 Byetta [package insert]. Wilmington, DE; AstraZeneca; December 2018.
137 Bydureon [package insert]. Wilmington, DE; AstraZeneca; February 2019.
138 Bydureon BCise [package insert]. Wilmington, DE; AstraZeneca; July 2019.
139 Symlin [package insert]. Wilmington, DE; AstraZeneca; December 2019.
140 Januvia [package insert]. Whitehouse Station, NJ; Merck; August 2019.
141 Jentadueto [package insert]. Ridgefield, CT; Boehringer Ingelheim; July 2019.
142 Janumet [package insert]. Whitehouse Station, NJ; Merck; August 2019.
143 Janumet XR [package insert]. Whitehouse Station, NJ; Merck; August 2019.
144 Onglyza [package insert]. Princeton, NJ; Bristol-Myers Squibb; August 2015.
145 Qternmet XR [package insert]. Wilmington DE; AstraZeneca; January 2020.
146 Qtern [package insert]. Wilmington DE; AstraZeneca; January 2020.
147 Victoza [package insert]. Princeton, NJ; Novo Nordisk; June 2019.
148 Kombiglyze XR [package insert]. Wilmington DE; AstraZeneca; October 2019.
149 Tradjenta [package insert]. Ridgefield, CT; Boehringer Ingelheim; July 2019.
150 Tanzeum [package insert]. Wilmington, DE; GlaxoSmithKline; December 2017.
151 Glyxambi [package insert]. Ridgefield, CT; Boehringer Ingelheim; January 2020.
152 Trijardy XR [package insert]. Ridgefield, CT; Boehringer Ingelheim; January 2020.
153 Adlyxin [package insert]. Bridgewater, NJ; Sanofi-Aventis; July 2016.
154 Soliqua [package insert]. Bridgewater, NJ; Sanofi-Aventis; November 2019.
155 Xultophy [package insert]. Plainsboro, NJ; Novo Nordisk; November 2019.
156 Ozempic [package insert]. Plainsboro, NJ; Novo Nordisk; January 2020.
157 Steglujan [package insert]. Whitehouse Station, NJ; Merck; January 2020.
158 Ryblesus [package insert]. Plainsboro, NJ; Novo Nordisk; January 2020.
159 Symlin [package insert]. Wilmington, DE; AstraZeneca; December 2019.
160 Nesina [package insert]. Deerfield, IL; Takeda; June 2019.
161 Kazano [package insert]. Deerfield, IL; Takeda; June 2019.
162 Oseni [package insert]. Deerfield, IL; Takeda; June 2019.
163 Tradjenta [package insert]. Ridgefield, CT; Boehringer Ingelheim; July 2019.
164 Glyxambi [package insert]. Ridgefield, CT; Boehringer Ingelheim; January 2020.
165 Trijardy XR [package insert]. Ridgefield, CT; Boehringer Ingelheim; January 2020.
166 Jentadueto [package insert]. Ridgefield, CT; Boehringer Ingelheim; July 2019.
167 Jentadueto XR [package insert]. Ridgefield, CT; Boehringer Ingelheim; July 2019.
168 Onglyza [package insert]. Princeton, NJ; Bristol-Myers Squibb; August 2015.
169 Qternmet XR [package insert]. Wilmington DE; AstraZeneca; January 2020.
170 Qtern [package insert]. Wilmington DE; AstraZeneca; January 2020.
171 Kombiglyze XR [package insert]. Princeton, NJ; Bristol-Myers Squibb March 2012.
172 Januvia [package insert]. Whitehouse Station, NJ; Merck; August 2019.
173 Janumet [package insert]. Whitehouse Station, NJ; Merck; August 2019.

174 Janumet XR [package insert]. Whitehouse Station, NJ; Merck; August 2019.
175 Tanzeum [package insert]. Wilmington, DE; GlaxoSmithKline; December 2017.
176 Trulicity [package insert]. Indianapolis, IN; Eli Lilly; January 2019.
177 Byetta [package insert]. Wilmington, DE; AstraZeneca; December 2018.
178 Bydureon [package insert]. Wilmington, DE; AstraZeneca; February 2019.
179 Bydureon BCise [package insert]. Wilmington, DE; AstraZeneca; July 2019.
180 Victoza [package insert]. Princeton, NJ; Novo Nordisk; June 2019.
181 Adlyxin [package insert]. Bridgewater, NJ; Sanofi-Aventis; July 2016.
182 Soliqua [package insert]. Bridgewater, NJ; Sanofi-Aventis; November 2019.
183 Xultophy [package insert]. Plainsboro, NJ; Novo Nordisk; November 2019.
184 Ozempic [package insert]. Plainsboro, NJ; Novo Nordisk; January 2020.
185 Steglujan [package insert]. Whitehouse Station, NJ; Merck; January 2020.
186 Ryblesus [package insert]. Plainsboro, NJ. Novo Nordisk; January 2020.
187 Nesina [package insert]. Deerfield, IL; Takeda; June 2019.
188 Kazano [package insert]. Deerfield, IL; Takeda; June 2019.
189 Oseni [package insert]. Deerfield, IL; Takeda; June 2019.
190 Byetta [package insert]. Wilmington, DE; AstraZeneca; December 2018.
191 Bydureon [package insert]. Wilmington, DE; AstraZeneca; February 2019.
192 Bydureon BCise [package insert]. Wilmington, DE; AstraZeneca; July 2019.
193 Symlin [package insert]. Wilmington, DE; AstraZeneca; December 2019.
194 Januvia [package insert]. Whitehouse Station, NJ; Merck; August 2019.
195 Janumet [package insert]. Whitehouse Station, NJ; Merck; August 2019.
196 Onglyza [package insert]. Wilmington DE; AstraZeneca; July 2019.
197 Qtern [package insert]. Wilmington DE; AstraZeneca; January 2020.
198 Qternmet XR [package insert]. Wilmington DE; AstraZeneca; January 2020.
199 Victoza [package insert]. Princeton, NJ; Novo Nordisk; June 2019.
200 Kombiglyze XR [package insert]. Wilmington DE; AstraZeneca; October 2019.
201 Tradjenta [package insert]. Ridgefield, CT; Boehringer Ingelheim; July 2019.
202 Jentadueto [package insert]. Ridgefield, CT; Boehringer Ingelheim; July 2019.
203 Tanzeum [package insert]. Wilmington, DE; GlaxoSmithKline; December 2017.
204 Trulicity [package insert]. Indianapolis, IN; Eli Lilly; January 2019.
205 Glyxambi [package insert]. Ridgefield, CT; Boehringer Ingelheim; January 2020.
206 Trijardy XR [package insert]. Ridgefield, CT; Boehringer Ingelheim; January 2020.
207 Adlyxin [package insert]. Bridgewater, NJ; Sanofi-Aventis. July 2016.
208 Soliqua [package insert]. Bridgewater, NJ; Sanofi-Aventis. November 2016.
209 Xultophy [package insert]. Plainsboro, NJ; Novo Nordisk. November 2016.
210 Ozempic [package insert]. Plainsboro, NJ. Novo Nordisk; January 2020.
211 Steglujan [package insert]. Whitehouse Station, NJ; Merck; January 2020.
212 Ryblesus [package insert]. Plainsboro, NJ; Novo Nordisk; January 2020.
213 Symlin [package insert]. Wilmington, DE; AstraZeneca; December 2019.
214 Nesina [package insert]. Deerfield, IL; Takeda; June 2019.
215 Kazano [package insert]. Deerfield, IL; Takeda; June 2019.
216 Oseni [package insert]. Deerfield, IL; Takeda; June 2019.
217 Tradjenta [package insert]. Ridgefield, CT; Boehringer Ingelheim; July 2019.
218 Glyxambi [package insert]. Ridgefield, CT; Boehringer Ingelheim; January 2020.
219 Trijardy XR [package insert]. Ridgefield, CT; Boehringer Ingelheim; January 2020.
220 Jentadueto [package insert]. Ridgefield, CT; Boehringer Ingelheim; July 2014.
221 Jentadueto XR [package insert]. Ridgefield, CT; Boehringer Ingelheim; July 2019.
222 Onglyza [package insert]. Princeton, NJ; Bristol-Myers Squibb; August 2015.
223 Qtern [package insert]. Wilmington DE; AstraZeneca; January 2020.
224 Qternmet XR [package insert]. Wilmington DE; AstraZeneca; January 2020.
225 Kombiglyze XR [package insert]. Wilmington DE; AstraZeneca; October 2019.
226 Januvia [package insert]. Whitehouse Station, NJ; Merck; August 2019.
227 Janumet [package insert]. Whitehouse Station, NJ; Merck; August 2019.
228 Janumet XR [package insert]. Whitehouse Station, NJ; Merck; August 2019.
229 Tanzeum [package insert]. Wilmington, DE; GlaxoSmithKline; December 2017.
230 Trulicity [package insert]. Indianapolis, IN; Eli Lilly; January 2019.
231 Byetta [package insert]. Wilmington, DE; AstraZeneca; December 2018.
232 Bydureon [package insert]. Wilmington, DE; AstraZeneca; February 2019.
233 Bydureon BCise [package insert]. Wilmington, DE; AstraZeneca; July 2019.
234 Victoza [package insert]. Princeton, NJ; Novo Nordisk; June 2019.
235 Adlyxin [package insert]. Bridgewater, NJ; Sanofi-Aventis; July 2016.
236 Soliqua [package insert]. Bridgewater, NJ; Sanofi-Aventis; November 2019.
237 Xultophy [package insert]. Plainsboro, NJ; Novo Nordisk; November 2019.

238 Ozempic [package insert]. Plainsboro, NJ; Novo Nordisk; January 2020.
239 Steglujan [package insert]. Whitehouse Station, NJ; Merck; January 2020.
240 Ryblesus [package insert]. Plainsboro, NJ; Novo Nordisk; January 2020.
241 Onglyza [package insert]. Princeton, NJ; Bristol-Myers Squibb; May 2013.
242 Food and Drug Administration. Guidance for Industry: Diabetes mellitus- Evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. Available at: https://www.fda.gov/drugs/guidances-drugs/all-guidances-drugs. Accessed February 26, 2020.
243 Food and Drug Administration. Guidance for Industry: Diabetes Mellitus. Developing Drugs and Therapeutic Biologics for Treatment and Prevention. Draft guidance. 2008. Available at: https://www.fda.gov/drugs/guidances-drugs/all-guidances-drugs. Accessed February 26, 2020.
244 Ratner RE, Dickey R, Fineman M, et al. Amylin replacement with pramlintide as an adjunct to insulin therapy improves long-term glycaemic and weight control in Type 1 diabetes mellitus: a 1-year, randomized controlled trial. Diabet Med. 2004; (11):1204-1212.
245 Edelman S, Garg S, Frias J, et al. A double-blind, placebo-controlled trial assessing pramlintide treatment in the setting of intensive insulin therapy in type 1 diabetes. Diabetes Care. 2006; 29(10):2189-2195.
246 Hollander PA, Levy P, Fineman MS, et al. Pramlintide as an adjunct to insulin therapy improves long-term glycemic and weight control in patients with type 2 diabetes: a 1-year randomized controlled trial. Diabetes Care. 2003; 26(3):784-790.
247 Oseni [package insert]. Deerfield, IL; Takeda; June 2019.
248 Rosenstock J, Inzucchi SE, Seufert J, et al. Initial combination therapy with alogliptin and pioglitazone in drug-naïve patients with type 2 diabetes. Diabetes Care. 2010;33:2406–2408.
249 Kazano [package insert]. Deerfield, IL; Takeda; June 2019.
250 Kazano [package insert]. Deerfield, IL; Takeda; June 2019.
251 Kazano [package insert]. Deerfield, IL; Takeda; June 2019.
252 Oseni [package insert]. Deerfield, IL; Takeda; June 2019.
253 Oseni [package insert]. Deerfield, IL; Takeda; June 2019.
254 White WB, Bakris GL, Bergenstal RM, et al. EXamination of cArdiovascular outcoMes with alogliptIN versus standard of carE in patients with type 2 diabetes mellitus and acute coronary syndrome (EXAMINE): a cardiovascular safety study of the dipeptidyl peptidase 4 inhibitor alogliptin in patients with type 2 diabetes with acute coronary syndrome. Am Heart J. 2011;162(4):620-626.e1. DOI: 10.1016/j.ahj.2011.08.004.
255 Scott LJ. Linagliptin: in type 2 diabetes mellitus. Drugs. 2011; 26;71(5):611-24.
256 Barnett AH. Linagliptin: a novel dipeptidyl peptidase 4 inhibitor with a unique place in therapy. Adv Ther. 2011; 28(6):447-59.
257 Gomis R, Espadero RM, Jones R, et al. 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(7):653-661.
258 Lewin AJ, Arvay L, Liu D, et al. Efficacy and tolerability of linagliptin added to a sulfonylurea regimen in patients with inadequately controlled type 2 diabetes mellitus: an 18-week, multicenter, randomized, double-blind, placebo-controlled trial. Clin Ther. 2012;34(9):1909-19.
259 Rosenstock J, Perkovic V, Johansen OD, et al. JAMA. 2019;321(1):69-79. DOI: 10.1001/jama.2018.18269. Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: the CARMELINA randomized clinical trial. JAMA. 2019; 321(1):69-79. DOI: 10.1001/jama.2018.18269.
260 Rosenstock J, Kahn SE, Johansen OE, et al. Effect of linagliptin vs glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes: the CAROLINA randomized clinical trial. JAMA. 2019 Sep 19. DOI: 10.1001/jama.2019.13772. [Epub ahead of print]
261 Groop PH, Cooper ME, Perkovic V, et al. Linagliptin and its effects on hyperglycaemia and albuminuria in patients with type 2 diabetes and renal dysfunction: the randomized MARLINA-T2D trial. Diabetes Obes Metab. 2017 Nov;19(11):1610-1619. DOI: 10.1111/dom.13041.
262 Glyxambi [package insert]. Ridgefield, CT; Boehringer Ingelheim; January 2020.
263 Zinman B, Wanner C, Lachin JM, et. al, Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015; 373: 2117-2128. DOI: 10.1056/NEJMoa1504720.
264 Jentadueto [package insert]. Ridgefield, CT; Boehringer Ingelheim; July 2019.
265 Jentadueto [package insert]. Ridgefield, CT; Boehringer Ingelheim; July 2019.
266 Jentadueto [package insert]. Ridgefield, CT; Boehringer Ingelheim; July 2019.
267 Relative bioavailability of 2 fixed dose combinations of empagliflozin/linagliptin/metformin extended release compared with single tablets. Available at: https://clinicaltrials.gov/ct2/show/NCT02821910. Accessed May 27, 2020.
268 Jentadueto XR [package insert]. Ridgefield, CT; Boehringer Ingelheim; July 2019.
269 Rosenstock J, Aguilar-Salinas C, Klein E, et al. Effect of saxagliptin monotherapy in treatment-naïve patients with type 2 diabetes. Curr Med Res Opin. 2009; 25(10):2401-11.
270 Chacra AR, Tan GH, Apanovitch A, et al. Saxagliptin added to a submaximal dose of sulphonylurea improves glycaemic control compared with uptitration of sulphonylurea in patients with type 2 diabetes: a randomised controlled trial. Int J Clin Pract. 2009; 63(9):1395-1406.
271 Jadzinsky M, Pfützner A, Paz-Pacheco E, et al. Saxagliptin given in combination with metformin as initial therapy improves glycaemic control in patients with type 2 diabetes compared with either monotherapy: a randomized controlled trial. Diabetes Obes Metab. 2009; 11(6):611-622.
272 Defronzo RA, Hissa MN, Garber AJ, et al. The Efficacy and Safety of Saxagliptin When Added to Metformin Therapy in Patients With Inadequately Controlled Type 2 Diabetes on Metformin Alone. Diabetes Care. 2009; 32(9):1649-55.
273 Hollander P, Li J, Allen E, et al for the CV282-03 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; 94(12):4810-9.
274 Onglyza [package insert]. Wilmington DE; AstraZeneca; July 2019.
275 Onglyza [package insert]. Wilmington DE; AstraZeneca; July 2019.
276 Onglyza [package insert]. Wilmington DE; AstraZeneca; July 2019.
277 Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. NEJM 2013; 369:1317-1326. DOI: 10.1056/NEJMoa1307684.
278 Qtern [package insert]. Wilmington DE; AstraZeneca; January 2020.
279 Qternmet XR [package insert]. Wilmington DE; AstraZeneca; January 2020.

280 Charbonnel B, Karasik A, Liu J, et al for the 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; 29(12):2638-43.
281 Raz I, Chen Y, Wu M, et al. Efficacy and safety of sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes. Curr Med Res Opin. 2008; 24(2):537-50.
282 Januvia [package insert]. Whitehouse Station, NJ; Merck; August 2019.
283 Bethal MA, Engel SS, Green JB, et al. Assessing the safety of sitagliptin in older participants in the trial evaluating cardiovascular outcomes with sitagliptin (TECOS). Diabetes Care. 2017; 40(4):494-501. DOI: 10.2337/dc16-1135.
284 Green JB, Bethel A, Armstrong PW, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2015; 373:232-42. DOI: 10.1056/NEJMoa1501352.
285 Scott R, Morgan J, Zimmer Z, et al. A randomized clinical trial of the efficacy and safety of sitagliptin compared with dapagliflozin in patients with type 2 diabetes mellitus and mild renal insufficiency: The CompoSIT-R study. Diabetes Obes Metab. 2018;20(12):2876-2884. DOI: 10.1111/dom.13473.
286 ClinicalTrials.gov. NCT02532855. Available at: https://clinicaltrials.gov/ct2/show/results/NCT02532855?view=results. Accessed February 26, 2020.
287 Goldstein BJ, Feinglos MN, Lunceford JK, et al. 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; 30(8):1979-1987.
288 Scheen AJ, Charpentier G, Ostgren CJ, et al. Efficacy and safety of saxagliptin in combination with metformin compared with sitagliptin in combination with metformin in adult patients with type 2 diabetes mellitus. Diabetes Metab Res Rev. 2010; 26(7):540-9.
289 Nauck MA, Meininger G, Sheng D, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. Diabetes Obes Metab. 2007; 9(2):194-205.
290 Scott R, Loeys T, Davies MJ, et al. Efficacy and safety of sitagliptin when added to ongoing metformin therapy in patients with type 2 diabetes. Diabetes Obes Metab. 2008; 10(10):959-969.
291 Rosenstock J, Brazg R, Andryuk PJ, et al. 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; 28(10):1556-1568.
292 Miller S, Krumins T, Zhou H, et al. Ertugliflozin and sitagliptin co-initiation in patients with type 2 diabetes: the VERTIS SITA randomized study. Diabetes Ther. 2018;9(1):253-268. DOI: 10.1007/s13300-017-0358-0.
293 Pratley RE, Eldor R, Raji A, et al. Ertugliflozin plus sitagliptin versus either individual agent over 52 weeks in patients with type 2 diabetes mellitus inadequately controlled with metformin: the VERTIS FACTORIAL randomized trial. Diabetes Obes Metab. 2018; 20(5):1111-1120. DOI: 10.1111/dom.13194.
294 Janumet [package insert]. Whitehouse Station, NJ; Merck; August 2019.
295 Janumet XR [package insert]. Whitehouse Station, NJ; Merck; August 2019.
296 Janumet [package insert]. Whitehouse Station, NJ; Merck; August 2019.
297 Janumet XR [package insert]. Whitehouse Station, NJ; Merck; August 2019.
298 Trulicity [package insert]. Indianapolis, IN; Eli Lilly; January 2019.
299 Umpierrez G, Tote Povedano S, Perez Manghi F, et al. Efficacy and safety of dulaglutide monotherapy versus metformin in type 2 diabetes in a randomized controlled trial (AWARD-3). Diabetes Care. 2014;37(8):2168-76. DOI: 10.2337/dc13-2759.
300 Nauck M, Weinstock RS, Umpierrez GE, et al. Efficacy and safety of dulaglutide versus sitagliptin after 52 weeks in type 2 diabetes in a randomized controlled trial (AWARD-5). Diabetes Care. 2014;37(8):2149-58. DOI: 10.2337/dc13-2761.
301 Trulicity [package insert]. Indianapolis, IN; Eli Lilly; January 2019.
302 Wysham C, Blevins T, Arakaki R, et al. Efficacy and safety of dulaglutide added onto pioglitazone and metformin versus exenatide in type 2 diabetes in a randomized controlled trial (AWARD-1). Diabetes Care. 2014;37(8):2159-67. DOI: 10.2337/dc13-2760.
303 Trulicity [package insert]. Indianapolis, IN; Eli Lilly; January 2019.
304 Dungan KM, Povedano ST, Forst T, et al. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. Lancet. 2014; 11;384(9951):1349-57. DOI: 10.1016/S0140-6736(14)60976-4.
305 Tuttle KR, Lakshmanan MC, Rayner B, et al. Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial. Lancet. 2018; 6(8):605-617. DOI: 10.1016/S2213-8587(18)30104-9.
306 Trulicity [package insert]. Indianapolis, IN; Eli Lilly; January 2019.
307 Buse JB, Henry RR, Han J, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. Diabetes Care. 2004; 27(11):2628-2635.
308 DeFronzo RA, Ratner RE, Han J, et al. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. Diabetes Care. 2005; 28(5):1092-1100.
309 Kendall DM, Riddle MC, Rosenstock J, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. Diabetes Care. 2005; 28(5):1083-1091.
310 Buse JB, Bergenstal RM, Glass LC, et al. Use of twice-daily exenatide in basal insulin–treated patients with type 2 diabetes: a randomized, controlled trial. Ann Intern Med. 2011;154.
311 Heine RJ, Van Gaal LF, Johns D, et al. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. Ann Intern Med. 2005; 143(8):559-569.
312 Barnett AH, Burger J, Johns D, et al. Tolerability & efficacy of exenatide and titrated insulin glargine in adult patients with type 2 diabetes previously uncontrolled with metformin or a sulfonylurea: a multinational, randomized, open-label, two period, crossover noninferiority trial. Clin Ther. 2007; 29(11):2333-2348.
313 Guja C, Frias JP, Somogyi A, et al. Effect of exenatide QW or placebo, both added to titrated insulin glargine, in uncontrolled type 2 diabetes: The DURATION-7 randomized study. Diabetes Obes Metab. 2018; 20(7):1602-1614. DOI: 10.1111/dom.13266.
314 Frías JP, Guja C, Hardy E, et al. Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised controlled trial. Lancet Diabetes Endocrinol. 2016;4(12):1004-1016. DOI: 10.1016/S2213-8587(16)30267-4.

315 Drucker DJ, Buse JB, Taylor K, et al. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. Lancet. 2008; 372(9645):1240-1250.
316 Buse JB, Drucker DJ, Taylor KL, et al. DURATION-1: Exenatide once weekly produces sustained glycemic control and weight loss over 52 weeks. Diabetes Care. 2010;33(6):1255-61. DOI: 10.2337/dc09-1914.
317 Wysham CH, MacConnell LA, Maggs DG, et al. Five-year efficacy and safety data of exenatide once weekly: long-term results from the DURATION-1 randomized clinical trial. Mayo Clin Proc. 2015; 90(3): 356-65. DOI: 10.1016/j.mayocp.2015.01.008.
318 Bydureon [package insert]. Wilmington, DE; AstraZeneca; February 2019.
319 Blevins T, Pullman J, Malloy J, et al. DURATION 5. Exenatide once-weekly resulted in greater improvements in glycemic control compared with exenatide twice-daily in patients with type 2 diabetes. Clin Endocrinol Metab. 2011; 96(5):1301. DOI: 10.1210/jc.2010-2081.
320 Buse JB, Nauck M, Forst T, et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomized, open-label study. Lancet. 2013; 381(9861):117-24.
321 Bergenstal RM, Wysham C, Macconell L, et al. Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial. Lancet. 2010;376(9739):431-9. DOI: 10.1016/S0140-6736(10)60590-9.
322 Gadde KM, Vetter ML, Iqbal N, et al. Efficacy and safety of autoinjected exenatide once-weekly suspension versus sitagliptin or placebo with metformin in patients with type 2 diabetes: The DURATION-NEO-2 randomized clinical study. Diabetes Obes Metab. 2017;19(7):979-988. DOI: 10.1111/dom.12908.
323 Holman RR, Bethel MA, Mentz RJ, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2017;377(13):1228-1239. DOI: 10.1056/NEJMoa1612917.
324 Garber A, Henry R, Ratner R, et al. LEAD-3 (mono) study group. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. Lancet. 2009; 373(9662):473-481.
325 Victoza [package insert]. Princeton, NJ; Novo Nordisk; June 2019.
326 Marre M, Shaw J, Brandle M, et al. LEAD-1 SU study group. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU). Diabet Med. 2009; 26(3): 268-278.
327 Russell-Jones D, Vaag A, Schmitz O, et al. LEAD-5 met+SU study group. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. Diabetologia. 2009; 52(10):2046-2055.
328 Zinman B, Gerich J, Buse JB, et al. LEAD-4 study investigators. Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). Diabetes Care. 2009; 32(7):1224-1230.
329 Victoza [package insert]. Princeton, NJ; Novo Nordisk; June 2019.
330 Buse JB, Rosenstock J, Sesti G, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). Lancet. 2009; 374(9683):39-47.
331 Pratley RE Nauck M Bailey T et al. 1860-LIRA-DPP-4 Study Group. Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. Lancet. 2010; 375(9724):1447-1456.
332 Pratley RE Nauck M Bailey T et al. One year of liraglutide treatment offers sustained and more effective glycaemic control and weight reduction compared with sitagliptin, both in combination with metformin, in patients with type 2 diabetes: a randomised, parallel-group, open-label trial. Int J Clin Pract. 2011; 65(4): 397–407.
333 DeVries JH, Bain SC, Rodbard HW, et al. Liraglutide-Detemir Study Group. Sequential intensification of metformin treatment in type 2 diabetes with liraglutide followed by randomized addition of basal insulin prompted by A1C targets. Diabetes Care. 2012; 35(7):1446-54.
334 Tamborlane WV, Barrientos-Perez M, Fainberg U, et al. Liraglutide in children and adolescents with type 2 diabetes. N Engl J Med 2019; 381:637-646. DOI: 10.1056/NEJMoa1903822
335 Victoza [package insert]. Princeton, NJ; Novo Nordisk; June 2019.
336 Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. NEJM. 2016;375(4):311-322.
337 Xultophy [package insert]. Plainsboro, NJ. Novo Nordisk; November 2019.
338 Xultophy [package insert]. Plainsboro, NJ; Novo Nordisk. November 2016.
339 Lingvay I, Pérez Manghi F, García-Hernández P, et. al. Effect of insulin glargine up-titration vs insulin degludec/liraglutide on glycated hemoglobin levels in patients with uncontrolled type 2 diabetes: The DUAL V randomized clinical trial. JAMA. 2016; 315(9): 898-907. DOI: 10.1001/jama.2016.1252.
340 Xultophy [package insert]. Plainsboro, NJ; Novo Nordisk; November 2019.
341 Xultophy [package insert]. Plainsboro, NJ; Novo Nordisk; November 2019.
342 Xultophy [package insert]. Plainsboro, NJ; Novo Nordisk; November 2019.
343 Rosenstock J, et al. Efficacy and safety of lixisenatide once daily versus exenatide twice daily in type 2 diabetes inadequately controlled on metformin. Diabetes Care. 2013;36(10):2945-51. DOI: 10.2337/dc12-2709.
344 Pfeffer MA, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med. 2015:373(23):2247-57. DOI: 10.1056/NEJMoa1509225.
345 Soliqua [package insert]. Bridgewater, NJ; Sanofi-Aventis. November 2016.
346 Aroda VR, Rosenstock J, Wysham C, et al. Efficacy and safety of Lixilan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide in type 2 diabetes inadequately controlled on basal insulin and metformin: The Lixilan-L randomized trial. Diabetes Care 2016, 39(11): 1972-1980. DOI: 10.2337/dc16-1495**.**
347 Rosenstock J, Aronson R, Grunberger G, et al. Benefits of LixiLan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide, versus insulin glargine and lixisenatide monocomponents in type 2 diabetes inadequately controlled with oral agents: The LixiLan-O randomized trial. Diabetes Care 2016 Aug; dc160917.DOI: 10.2337/dc16-0917**.**
348 Sorli C, Harashima SI, Tsoukas GM, et al. efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomized, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial. Lancet Diabet Endocrinol. 2017; 5(4): 251-260. DOI: 10.1016/S2213-8587(17)30013-X.

349 Ahren B, Masmiquel L, Kumar L, et al. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. Lancet Diabetes Endocrinol. 2017; 5(5): 341-354. DOI: 10.1016/S2213-8587(17)30092-X.
350 Ahmann AJ, Capehorn M, Charpentier G, et al. Efficacy and safety of once-weekly semaglutide versus exenatide ER in subjects with type 2 diabetes (SUSTAIN 3): a 56-week, open-label, randomized clinical trial. Diabetes Care. 2018;41(2):258-266. DOI: 10.2337/dc17-0417.
351 Aroda VR, Bain SC, Cariou B, et al. Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. Lancet Diabetes Endocrinol. 2017; 5(5): 355-366. DOI: 10.1016/S2213-8587(17)30085-2.
352 Rodbard H, Lingvay I, Reed J, et al. Efficacy and safety of semaglutide once-weekly vs placebo as add-on to basal insulin alone or in combination with metformin in subjects with type 2 diabetes (SUSTAIN 5). Diabetologia. 2016; 59: S364-5 [abstract].
353 Marso SP, Bain SC, Consoli A, et al for the SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016; 375(19): 1834-1844. DOI: 10.1056/NEJMoa1607141.
354 Pratley RE, Aroda VR, Lingvay I, et al. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. The Lancet. 2018;6(4):275-286. DOI: 10.1016/S2213-8587(18)30024-X.
355 Lingvay I, Desouza CV, Lalic KS, et al. A 26-week randomized controlled trial of semaglutide once daily versus liraglutide and placebo in patients with type 2 diabetes suboptimally controlled on diet and exercise with or without Metformin. Diabetes Care 2018;41(9):1926-1937. DOI 10.2337/dc17-2381.
356 Dose-finding of Semaglutide Administered Subcutaneously Once Daily Versus Placebo and Liraglutide in Subjects with Type 2 Diabetes. Available at: https://clinicaltrials.gov/ct2/show/NCT02461589. Accessed February 26, 2020.
357 Lingvay I, Catarig AM, Frias JP, et al. Efficacy and safety of once-weekly semaglutide versus daily canagliflozin as add-on to metformin in patients with type 2 diabetes (SUSTAIN 8): a double-blind, phase 3b, randomised controlled trial. Lancet. 2019;7(11):834-844.
358 Ryblesus [package insert]. Plainsboro, NJ; Novo Nordisk; January 2020.
359 Ryblesus [package insert]. Plainsboro, NJ; Novo Nordisk; January 2020.
360 Rodbard HW, Rosenstock J, Canani LH. Oral semaglutide versus empagliflozin in patients with type 2 diabetes uncontrolled on metformin: the PIONEER2 Trial. Diabetes Care. 2019; 42(12):2272-2281. DOI: 10.2337/dc19-0883.
361 Ryblesus [package insert]. Plainsboro, NJ; Novo Nordisk; January 2020.
362 Rosenstock J, Allison D, Birkenfeld AL, et al. Effect of additional oral semaglutide vs sitagliptin on glycated hemoglobin in adults With type 2 diabetes uncontrolled with metformin alone or with sulfonylurea. The PIONEER 3 randomized clinical trial. JAMA.2019;321(15):1466–1480. DOI:10.1001/jama.2019.2942.
363 Pieber TR, Bode B, Mertens A, et al. Efficacy and safety of oral semaglutide with flexible dose adjustment versus sitagliptin in type 2 diabetes (PIONEER7): a multicentre, open-label, randomised, phase3a trial. Lancet Diabetes Endocrinol. 2019;7(7):528-539. DOI: 10.1016/S2213-8587(19)30194-9.
364 Ryblesus [package insert]. Plainsboro, NJ; Novo Nordisk; January 2020.
365 Pratley R, Amod A, Hoff ST, et al. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER4): a randomised, double-blind, phase 3a trial. Lancet.2019;394(10192):39-50. DOI: 10.1016/S0140-6736(19)31271-1.
366 Ryblesus [package insert]. Plainsboro, NJ; Novo Nordisk; January 2020.
367 Mosenzon O, Blicher TM, Rosenlund S, et al. Efficacy and safety of oral semaglutide in patients with type 2 diabetes and moderate renal impairment (PIONEER 5): a placebo-controlled, randomised, phase 3a trial. Lancet Diabetes Endocrinol. 2019;7(7):515-527. DOI: 10.1016/S2213-8587(19)30192-5.
368 Ryblesus [package insert]. Plainsboro, NJ; Novo Nordisk; January 2020.
369 Zinman B, Aroda VR, Buse JB, et al. Efficacy, safety, and tolerability of oral semaglutide versus placebo added to insulin with or without metformin in patients with type 2 diabetes: The PIONEER 8 Trial. 2019;42(12):2262-2271. DOI: 10.2337/dc19-0898.
370 Ryblesus [package insert]. Plainsboro, NJ; Novo Nordisk; January 2020.
371 Husain MR, Birkenfeld A, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2019; 381:841-851. DOI: 10.1056/NEJMoa1901118.
372 Monami M, Marchionni N, Mannucci E. Glucagon-like peptide-1 receptor agonists in type 2 diabetes: a meta-analysis of randomized clinical trials. Eur J Endocrinol. 2009; 160(6):909-17.
373 Zaccardi F, Htike ZZ, Webb DR, et al. Benefits and harms of once-weekly glucagon-like peptide-1 receptor agonist treatments: a systematic review and network meta-analysis. Ann Intern Med. 2016;164:102-113.
374 Htike ZZ, Zaccardi F, Papamargaritis D, et al. Efficacy and safety of glucagon-like peptide-1 receptor agonists in type 2 diabetes: A systematic review and mixed-treatment comparison analysis. Diabetes Obes Metab. 2017;19(4):524-536. DOI: 10.1111/dom.12849.
375 Esposito K, Cozzolino D, Bellastella G, 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; 13(7):594-603.
376 Salvo F, Moore N, Arnaud M, et al. Addition of dipeptidyl peptidase-4 inhibitors to sulphonylureas and risk of hypoglycaemia: systematic review and meta-analysis. BMJ. 2016; 353: i2231. DOI: 10.1135/bmj.i2231.
377 Keshavarz K, Lotfi F, Sanati E, et al. Linagliptin versus sitagliptin in patients with type 2 diabetes mellitus: a network meta-analysis of randomized clinical trials. Daru. 2017; 25(1):23. DOI: 10.1186/s40199-017-0189-6.
378 Peterson SC, Berry AR. Effect of glucagon-like peptide-1 receptor agonists on all-cause mortality and cardiovascular outcomes: A meta-analysis. Curr Diabetes Rev. 2018;14(3):273-279. DOI: 10.2174/1573399813666170414101450.
379 Bethel MA, Patel RA, Merrill P, et al. Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a meta-analysis. Lancet Diabetes Endocrinol. 2018 Feb;6(2):105-113. DOI: 10.1016/S2213-8587(17)30412-6.