



# Hypoglycemics, Incretin Mimetics/Enhancers

## Therapeutic Class Review (TCR)

October 29, 2014

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## FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indications
<b>Amylin Analogue</b>		
pramlintide (Symlin®) <sup>1</sup>	Amylin	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)
<b>DPP-4 Enzyme Inhibitors</b>		
alogliptin (Nesina®) <sup>2</sup>	Takeda	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM)
alogliptin/metformin (Kazano®) <sup>3</sup>	Takeda	
alogliptin/ pioglitazone (Oseni®) <sup>4</sup>	Takeda	
linagliptin (Tradjenta™) <sup>5</sup>	Boehringer Ingelheim	Adjunct to diet and exercise to improve glycemic control in adults with T2DM
linagliptin/metformin (Jentadueto™) <sup>6</sup>	Boehringer Ingelheim	Adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both linagliptin and metformin is appropriate.
saxagliptin (Onglyza™) <sup>7</sup>	Bristol-Myers Squibb	Adjunct to diet and exercise to improve glycemic control in adults with T2DM
saxagliptin/metformin extended-release (Kombiglyze XR™) <sup>8</sup>	Bristol-Myers Squibb	Adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both saxagliptin and metformin is appropriate
sitagliptin (Januvia™) <sup>9</sup>	Merck Sharp & Dohme	Adjunct to diet and exercise to improve glycemic control in adults with T2DM; sitagliptin has been studied in combination with metformin, pioglitazone, glimepiride, and metformin with glimepiride
sitagliptin/metformin (Janumet™) <sup>10</sup>	Merck Sharp & Dohme	Adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both agents is appropriate
sitagliptin/metformin extended release (Janumet XR™) <sup>11</sup>	Merck	Adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both sitagliptin and metformin extended-release is appropriate
<b>GLP-1 Receptor Agonists</b>		
albiglutide (Tanzeum®) <sup>12</sup>	GlaxoSmithKline	▪ Adjunct to diet and exercise to improve glycemic control in adults with T2DM
dulaglutide (Trulicity™) <sup>13</sup>	Eli Lilly	▪ Adjunct to diet and exercise to improve glycemic control in adults with T2DM

**FDA-Approvals Indications (continued)**

Drug	Manufacturer	Indications
exenatide (Byetta™) <sup>14</sup>	Amylin/Lilly	<ul style="list-style-type: none"> <li>▪ Adjunct to diet and exercise to improve glycemic control in adults with T2DM who are taking metformin, a sulfonylurea, a thiazolidinedione (TZD), or a combination of metformin and a sulfonylurea or TZD but have not achieved adequate glycemic control</li> <li>▪ Add-on therapy to insulin glargine, with or without metformin and/or a TZD, in conjunction with diet and exercise for adults with type 2 diabetes who are not achieving adequate glycemic control on insulin glargine alone</li> </ul>
exenatide extended-release (Bydureon®) <sup>15</sup>	Amylin	<ul style="list-style-type: none"> <li>▪ Adjunct to diet and exercise to improve glycemic control in adults with T2DM</li> </ul>
liraglutide (Victoza®) <sup>16</sup>	Novo Nordisk	<ul style="list-style-type: none"> <li>▪ Adjunct to diet and exercise to improve glycemic control in adults with T2DM</li> </ul>

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

**Albiglutide (Tanzeum)**, exenatide (Byetta, Bydureon), and liraglutide (Victoza) have not been studied in combination with prandial insulin. **Dulaglutide (Trulicity)** and exenatide extended-release (Bydureon) have not been studied in combination with basal insulin.

**Albiglutide (Tanzeum)**, **dulaglutide (Trulicity)**, exenatide (Byetta, Bydureon), liraglutide (Victoza), linagliptin (Tradjenta, Jentaducto), saxagliptin (Onglyza), saxagliptin/metformin (Kombiglyze XR), sitagliptin (Januvia), sitagliptin/metformin (Janumet), sitagliptin/metformin (Janumet XR), linagliptin (Tradjenta), and linagliptin/metformin (Jentaducto) have not been studied in patients with a history of pancreatitis.

Do not coadminister exenatide (Byetta) and exenatide extended-release (Bydureon).

Sitagliptin/simvastatin (Juvisync™) has been voluntarily discontinued by Merck due to business reasons and not due to safety concerns. All products currently in distribution will reach expiration by October 2014.

**OVERVIEW**

Initial treatment for type 2 diabetes 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, type 2 diabetes is characterized by insufficient secretion of the neuroendocrine hormone amylin from the pancreatic beta-cells and insufficient incretin hormone stimuli from incretins, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Novel therapies target these areas and include synthetic hormones, incretin mimetics, and dipeptidyl peptidase-4 (DPP-4) inhibitors.

According to the American Diabetes Association (ADA) 2014 Standards of Medical Care in Diabetes and the 2012 ADA/European Association for the Study of Diabetes (EASD) Consensus Statement, selection of an antidiabetic medication should be based on patient-related variables (e.g., level of glycemic control, adherence to treatment) and agent-related variables, such as the degree and relative quickness with which the medication can lower blood glucose, adverse effect profile, and nonglycemic effects.<sup>17,18</sup> It is generally agreed that metformin, if not contraindicated and if tolerated, is the preferred first agent in the treatment of type 2 diabetes. If metformin cannot be used, another oral agent could be chosen, such as a sulfonylurea, pioglitazone, or a DPP-4 inhibitor; occasionally in cases where weight loss is seen as an essential aspect of therapy, initial treatment with a GLP-1 receptor agonist might be useful. If noninsulin monotherapy at maximal tolerated dose does not achieve or maintain the HbA1c target over three months, a second oral agent, a GLP-1 receptor agonist, or insulin should be added. On average, any second agent is typically associated with further reduction in HbA1c of approximately one percent.

In 2013, the American Academy of Clinical Endocrinologists (AACE) released an algorithm and consensus statement for type 2 diabetes which replaces the 2009 AACE/ACE diabetes algorithm for glycemic control.<sup>19</sup> A Treatment goal of HbA1c of  $\leq 6.5\%$  for healthy patients with low hypoglycemic risk is recommended; for patients with concurrent illness and at risk of hypoglycemia goal HbA1c is  $>6.5\%$  is appropriate. Lifestyle modification, including medically assisted weight loss, underlies all treatments. Choice of therapy should be based on cost, ease of use, other medication and patient risk factors, and the patient's initial HbA1c level. AACE suggests for patients with an HbA1c  $<7.5\%$  start with monotherapy; whereas patients with an HbA1c  $\geq 7.5\%$  begin with dual therapy. Patients with an HbA1c  $>9\%$  and no symptoms may start either dual or triple antihyperglycemic therapy; patients with an HbA1c  $>9\%$  with symptoms should begin insulin therapy with or without other agents. HbA1c should be reassessed every three 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. For patients  $<7.5\%$  at entry, monotherapy options that are considered safer are metformin, a GLP-1 receptor agonist, a DPP-4 inhibitor, or an alpha-glucosidase inhibitor. Medications to be used with caution, include sodium-dependent glucose cotransporter 2 (SGLT2) inhibitors, thiazolidinediones, and sulfonylureas.

## PHARMACOLOGY<sup>20,21</sup>

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 type 1 or type 2 diabetes using 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 analog of amylin, affects the rate of glucose appearance 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 lowers glucagon secretion from

pancreatic alpha cells, leading to reduced hepatic glucose production. GLP-1 also slows gastric emptying. GIP and GLP-1 are rapidly inactivated by the DPP-4 enzyme.

Incretins enhance glucose-dependent insulin secretion and exhibit other hypoglycemic actions following release into the circulation from the gut. The GLP-1 agonist agents, **albiglutide (Tanzeum), dulaglutide (Trulicity)**, exenatide (Byetta, Bydureon) and liraglutide (Victoza), enhance glucose-dependent insulin secretion by the beta cell, suppress inappropriately elevated glucagon secretion, and slow gastric emptying. Exenatide (Byetta) is considered to be a short-acting GLP-1 receptor agonist and is dose twice daily.<sup>22,23</sup> The exenatide extended-release (ER) formulation releases exenatide from microspheres over a period of about 10 weeks and allowing for once weekly dosing. **The longer half-life of albiglutide and liraglutide is due, at least in part, to a decreased DPP-4 degradation in the body; making them appropriate for once weekly dosing.**<sup>24</sup> **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.**<sup>25</sup>

Sitagliptin (Januvia), saxagliptin (Onglyza), linagliptin (Tradjenta), and alogliptin (Nesina), are DPP-4 enzyme inhibitors. Inhibiting 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 glucagon-like peptide-1 (GLP-1), thereby lowering glucose levels. Sitagliptin/metformin (Janumet), sitagliptin/metformin ER (Janumet XR), saxagliptin/metformin ER (Kombiglyze XR), linagliptin/metformin (Jentaducto), alogliptin/metformin (Kazano) 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 thiazolidinediones (TZD).<sup>26</sup> Pioglitazone is a peroxisome proliferator-activated receptor-gamma agonist that improves insulin sensitivity in muscle and adipose tissue and inhibits hepatic gluconeogenesis.

## PHARMACOKINETICS

Drug	Peak (hrs)	Half-life (hrs)	Metabolism	Excretion
<b>Amylin Analogue</b>				
pramlintide (Symlin) <sup>27</sup>	0.33	0.8	Primarily by kidneys to des-lys pramlintide (active metabolite)	--
<b>DPP-4 Enzyme Inhibitors</b>				
saxagliptin (Onglyza) <sup>28,29</sup>	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) <sup>30,31</sup>	1-4	12.4	Primarily by CYP3A4 (minor)	Urine: 87% ; Feces 13%
linagliptin (Tradjenta) <sup>32</sup>	1.5	12	90% unchanged, no active metabolite	Urine: 5% Feces: 80%
metformin <sup>33,34,35</sup>	4-8	6.2	None	Excreted unchanged in the urine
pioglitazone <sup>36</sup>	2	3-7 (parent drug) 16-24 (metabolites)	Extensive hydroxylation and oxidation; two major active metabolites	Urine: 15-30% Feces: nr
<b>GLP-1 Receptor Agonists</b>				
albiglutide (Tanzeum) <sup>37</sup>	3-5 days	5 days	Protein catabolism	nr
alogliptin (Nesina) <sup>38</sup>	1-2	21	Active metabolite: N-demethylated alogliptin <1% of the parent compound	Urine: 76% Feces: 13%
dulaglutide (Trulicity) <sup>39</sup>	24-72	5 days	Protein catabolism	nr
exenatide (Byetta) <sup>40</sup>	2.1	2.4	Predominantly by the kidneys	Predominantly by the kidneys
exenatide extended-release (Bydureon) <sup>41,42</sup>	Peak 1: 2 weeks Peak 2: 6-7 Weeks	4 days	Predominantly by the kidneys	Predominantly by the kidneys
liraglutide (Victoza) <sup>43</sup>	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

In bioequivalence studies, alogliptin/metformin (Kazano), alogliptin/pioglitazone (Oseni), sitagliptin/metformin (Janumet), sitagliptin/metformin ER (Janumet XR), saxagliptin/metformin ER (Kombiglyze XR), and (linagliptin/metformin (Jentadueto) were found to be bioequivalent to the single agents administered together. After administration of Janumet XR tablets with a high-fat breakfast, the AUC for sitagliptin was not altered and the mean  $C_{max}$  was decreased by 17 percent, although the median  $T_{max}$  was unchanged relative to the fasted state. The AUC for metformin increased 62 percent, the  $C_{max}$  decreased by nine percent and the median  $T_{max}$  occurred two hours later relative to the fasted state.<sup>44</sup> Administration of linagliptin 2.5 mg/metformin hydrochloride 1000 mg fixed-dose combination with food resulted in no change in overall exposure of linagliptin. There was no change in metformin AUC; however, mean peak serum concentration of metformin was decreased by 18 percent when administered with food. A delayed time-to-peak serum concentrations by two hours was observed for metformin under fed conditions. These changes are not likely to be clinically significant.<sup>45,46</sup>

It is presumed that most of an oral pioglitazone dose is excreted into the bile either unchanged or as metabolites and eliminated in the feces.

## CONTRAINDICATIONS/WARNINGS<sup>47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62</sup>

Each product in this class is contraindicated in patients who have a known hypersensitivity to any of its components.

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with any antidiabetic agent.

In March 2013, the FDA published an alert stating that patients with type 2 diabetes treated with DPP-4 inhibitors or GLP-1 agonists may be at increased risk of pancreatitis and pre-cancerous cellular changes (pancreatic duct metaplasia).<sup>63</sup> This warning is based on examination of a small number of pancreatic tissue specimens taken from patients after death from unspecified causes. In addition, in March 2014, based on review of toxicology studies which showed no incretin-associated adverse effects on the pancreas, the FDA and EMA (European Medicines Agency) announced that they have not reached a final conclusion about a causal relationship between use of incretin-based drugs and pancreatitis or pancreatic cancer.<sup>64</sup> Both agencies continue to investigate this safety signal.

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.<sup>65</sup> 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 were unable to definitively rule out the possibility that exposure to the drugs themselves could act as an initiating event or could be tumor-promoting. Rather than focusing on the potential hazards of specific anti-diabetic agents, the consensus statement emphasizes the importance of better managing obesity, which has been linked with different malignancies, including breast, endometrial, pancreatic, and colorectal cancer.

A recent study concluded that treatment with the GLP-1 based therapies, sitagliptin and exenatide, each with current (therapy within 30 days) and recent use (more than 30 days and less than two years) are associated with an increased risk of hospitalization for acute pancreatitis (adjusted odds ratio, 2.24 [95% CI, 1.36-3.68]) and (2.01 [1.37-3.18]), respectively.<sup>66</sup> In a joint response to this JAMA Internal

Medicine 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.<sup>67</sup>

## Amylin Analogue

Pramlintide is contraindicated in patients with gastroparesis or hypoglycemia unawareness. Pramlintide also carries a black box 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 greater than 9 percent or who require use of drugs that stimulate gastrointestinal (GI) motility.

## DPP-4 Enzyme Inhibitors

DPP-4 inhibitors have been associated with serious hypersensitivity reactions in postmarketing reports of patients treated with these medications. Reported reactions have varied in severity and include anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, exfoliative skin conditions such as Stevens-Johnson syndrome, elevations in hepatic enzymes, and pancreatitis. Onset of these reactions has occurred after the initial dose to within the first three 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 monitoring accordingly.

There have been postmarketing 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 with a history of pancreatitis are at an increased risk for development of pancreatitis.

The use of DPP-4 inhibitors 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 two agents are used together.

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

**SAVOR TIMI-53:<sup>68</sup> A recent randomized, double-blind, placebo-controlled phase IV, manufacturer-funded trial evaluated cardiovascular (CV) outcomes with saxagliptin (5 mg daily or 2.5 mg daily in patients with an estimated glomerular filtration rate of  $\leq 50$  mL/minute). Patients (n=16,492) were followed for a mean of 2.1 years. The study found that in patients with type 2 diabetes with a history of, or at risk for, CV events, saxagliptin had no effect on the primary efficacy endpoint of composite of CV death, myocardial infarction (MI), or ischemic stroke (hazard ratio [HR] with saxagliptin, 1.00; 95% CI, 0.89 to 1.12; p=0.99 for superiority; p<0.001 for noninferiority). The secondary efficacy endpoint of composite of CV death, MI, stroke; hospitalization for unstable angina, heart failure, or coronary revascularization, occurred in 12.8 percent and 12.4 percent, of the saxagliptin and placebo groups,**

respectively (HR, 1.02; 95% CI, 0.94 to 1.11; p=0.66). However, the rate of hospitalization for heart failure was significantly increased (p=0.007). The study authors recommend further investigation of this increased rate of heart failure. Rates of adjudicated cases of acute and chronic pancreatitis were similar.

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 cardiovascular drug therapy.<sup>69</sup> The primary endpoint of the trial was a composite of CV death, nonfatal MI, and nonfatal stroke, and similar to SAVOR, the study showed alogliptin no worse than placebo. Glycosylated hemoglobin levels were significantly reduced with alogliptin, a mean difference of -0.36 percent. No increase in hypoglycemia or any increased risk of cancer or pancreatitis were observed.

In February 2014, as a result of the SAVOR-TIMI 53 CV outcomes trial, the FDA announced that it is studying a possible association between use of the type 2 diabetes drug saxagliptin and heart failure.<sup>70</sup> The FDA is not advising patients to stop using saxagliptin, nor is it asking health care professionals to stop prescribing the DPP-4 inhibitor.

A national commercially insured US database was used to evaluate the effect of sitagliptin in patients with type 2 diabetes and heart failure.<sup>71</sup> In the analysis 7,620 patients were identified with incident HF and also having type 2 diabetes. 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. HF-specific hospital admission or death also was assessed. 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.

There have been postmarketing 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 reinitiating 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.

Alogliptin/metformin (Kazano) is contraindicated in patients with renal impairment (serum creatinine levels greater than or equal to 1.5 mg/dL for men; greater than or equal to 1.4 mg/dL for women; or abnormal creatinine clearance [CrCl]) or metabolic acidosis, including lactic acidosis.

Combination products containing metformin (Janumet, Janumet XR, Jentaduetto, Kazano, Kombiglyze XR,) carry a boxed warning for lactic acidosis due to the accumulation of the metformin component. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure. Symptoms include malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. If acidosis is suspected, DPP-4 inhibitor/metformin therapy should be discontinued and the patient hospitalized immediately. Metformin is substantially secreted by the kidney. Metformin is contraindicated in patients with a serum creatinine greater than or equal to 1.5 mg/dL (males) or greater than or equal to 1.4 mg/dL (females). 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.

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.

Patients treated with metformin-containing regimens should be advised to avoid excessive alcohol intake.

There have been reports of incompletely dissolved sitagliptin/metformin ER (Janumet XR) tablets being eliminated in the feces.<sup>72</sup> It is not known if tablets eliminated contain drug. If a patient reports repeated tablets in stool, assess adequacy of glycemic control.

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 test is performed prior to beginning therapy and, if abnormal, therapy should be started with caution.

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

## GLP-1 Receptor Agonists

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

Albiglutide, dulaglutide, and liraglutide are contraindicated in patients with either personal or family history of medullary thyroid carcinoma (MTC) or patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Exenatide extended-release (Bydureon) has a black box warning regarding the risk of thyroid C-cell tumors (MTC) and Multiple Endocrine Neoplasia syndrome type 2 (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 albiglutide and dulaglutide in clinical trials. Postmarketing reports of pancreatitis, including fatal and non-fatal hemorrhagic necrotizing pancreatitis, have occurred with exenatide (Bydureon, Byetta) and liraglutide use. After therapy initiation with either agent, 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. Albiglutide, dulaglutide, and exenatide (Bydureon, Byetta) have not been studied in patients with severe gastrointestinal disease, including severe gastroparesis; therefore are not recommended for patients with severe gastrointestinal disease. Liraglutide dosage is titrated during the first one to two weeks of therapy to reduce gastrointestinal symptoms.

Acute renal failure and worsening of chronic renal failure, which may warrant hemodialysis, has been reported post-marketing with GLP-1 receptor agonists. Some of these reports have been in patients without known underlying renal disease. Some of the events occurred in patients receiving one 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.

Hypersensitivity reactions, including anaphylaxis and angioedema, have been reported with GLP-1 agonist use. Patients with hypersensitivity reactions to exenatide should discontinue exenatide and other suspect medications and promptly seek medical advice.

Glucose lowering with GLP-1 agonists is not associated with an inherently high risk of hypoglycemia.<sup>73,74,75,76</sup> 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.

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 five and ten percent of subjects on albiglutide and liraglutide, respectively, formed antibodies to the drug; however efficacy and safety were not affected. No dulaglutide anti-drug antibodies were found in clinical pharmacology studies.<sup>77</sup>

### ***Risk Evaluation and Mitigation Strategies (REMS)***

Albiglutide (Tanzeum), dulaglutide (Trulicity), liraglutide (Victoza) and exenatide ER (Bydureon) are subject to a communication plan to inform healthcare providers and patients of the risk of acute pancreatitis, medullary thyroid carcinoma. Pramlintide (Symlin) is subject to a communication plan regarding the risk of severe hypoglycemia as it is used with insulin and the importance of insulin dose reduction

## **DRUG INTERACTIONS<sup>78,79,80,81,82,83,84,85,86,87,88,89,90,91,92</sup>**

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.

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 one hour before or two hours after pramlintide (Symlin). Pramlintide should also not be prescribed for patients taking other medications that alter gastric motility or absorption of nutrients.

In addition, the effect of GLP-1 inhibitors on gastric emptying time may reduce the extent and rate of absorption of orally administered drugs that are given concomitantly. Patients should take oral medications at least one hour before exenatide injection. In clinical trials, albiglutide, dulaglutide, and liraglutide 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.

When used in combination with metformin, no increase in the incidence of hypoglycemia was observed with GLP-1 agonists compared to placebo. However, use of albiglutide, dulaglutide, exenatide (including extended-release) or liraglutide with a sulfonyleurea or insulin may increase the incidence of hypoglycemia. A reduced dose of sulfonyleurea should be considered.

There are postmarketing 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 extended-release has not been studied with warfarin. Prothrombin time should be monitored more closely after initiation or change in exenatide (Byetta, Bydureon) therapy in patients also on warfarin. In clinical studies albiglutide did not significantly alter the effects of warfarin as measured by the INR.

Administration of exenatide (Byetta, Bydureon) decreased exposure to lovastatin by 40 percent and delayed the time to maximum serum concentration (T<sub>max</sub>) and decreased maximum serum concentration (C<sub>max</sub>) of lovastatin.

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

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 coadministered with a strong CYP2C8 inducer (e.g., rifampin).

Saxagliptin (Onglyza) is metabolized primarily by the cytochrome P450 3A4/5 (CYP3A4/5) enzyme. Drugs that are strong inhibitors of this enzyme can significantly increase the exposure to saxagliptin. The dose for saxagliptin should be limited to 2.5 mg when coadministered 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 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.

Sitagliptin (Januvia) is metabolized via the CYP450 enzymes but has low likelihood for causing drug interactions. Sitagliptin 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.

Concurrent use of metformin-containing products (Janumet, Janumet XR, Jentadueto, Kazano, and Kombiglyze XR) and carbonic anhydrase inhibitors should be used with caution since it could cause metabolic acidosis. Cationic drugs (e.g., amiloride, cimetidine, morphine, procainamide, quinidine, or triamterene) have the potential for interaction with metformin by competing for common renal transport systems. Such an interaction between metformin and oral cimetidine has been observed in normal healthy volunteers with a 60 percent increase in peak metformin plasma and whole blood concentrations. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and/or dose adjustment of alogliptin/metformin, linagliptin/metformin, sitagliptin/metformin, sitagliptin/metformin ER or saxagliptin/metformin ER and/or the interfering drug is recommended in patients who are taking cationic medications.

**ADVERSE EFFECTS**

Drug	Nausea	Vomiting	Diarrhea	Headache	Hypoglycemia	URI
<b>Amylin Analogue</b>						
pramlintide (Symlin) <sup>93</sup>	28-48 (12-17)	8-11 (4-7)	nr	5-13 (7)	4.7-16.8 (2.1-10.8)	nr
<b>DPP-4 Inhibitors</b>						
alogliptin (Nesina) <sup>94</sup>	nr	nr	nr	4.2 (2.5)	1.5 (1.6)	4.2 (2.1)
alogliptin/metformin (Kazano) <sup>95</sup>	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) <sup>96</sup>	nr	nr	nr	reported	0.8-3.8 (0.8)	4.1 (3.3)
linagliptin (Tradjenta) <sup>97</sup>	nr	nr	nr	5.7	7.6 (4.1)	2.4 (1.1)
linagliptin/metformin (Jentaduetto) <sup>98</sup>	reported	reported	6.3	nr	reported	nr
saxagliptin (Onglyza) <sup>99</sup>	nr	2.2-2.3 (1.3)	nr	6.5 (5.9)	4.0-5.6 (4.1)	7.7 (7.6)
saxagliptin/ metformin ER (Kombiglyze XR) <sup>100</sup>	nr	nr	6.9 (11.2)	7.5 (5.2)	3.4-7.8 (5)	nr
sitagliptin (Januvia) <sup>101</sup>	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/metformin (Janumet, Janumet XR) <sup>102,103</sup>	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)
<b>GLP-1 Receptor Agonists</b>						
albiglutide (Tanzeum®) <sup>104</sup>	11.1 (9.6)	4.2 (2.6)	13.1 (10.5)	nr	2 (2)	14.2 (13)
dulaglutide (Trulicity) <sup>105</sup>	12.4-21.1 (5.3)	6-12.7 (2.3)	8.9-12.6 (6.7)	nr	2.6-5.6 (0)	nr
exenatide (Byetta) <sup>106</sup>	8-44 (0-18)	4-13 (0-4)	≥1-13 (0-6)	9 (6)	3.8-35.7 (3.3-12.6)	nr
exenatide extended-release (Bydureon) <sup>107</sup>	11.3-27	10.8-11.3	9.3-20	6.1-9.9	0-20	nr
liraglutide (Victoza) <sup>108</sup>	28.4	10.9	17.1	9.1	3.6-27.4 (2.5-16.7)	9.5

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.

Hypoglycemia was reported more commonly in patients treated with combination of saxagliptin and sulfonylurea or insulin.

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

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

Other common adverse effects with exenatide extended-release (Bydureon) included gastroesophageal reflux (7.4 percent), constipation (6.3-10.1 percent), dyspepsia (5-7.3 percent), decreased appetite (5 percent) and fatigue (5.6-6.1 percent).

In five comparator-controlled 24-30 week trials, injection site reactions were observed more frequently in patients treated with exenatide extended-release (Bydureon; 17.1 percent) than in patients treated with exenatide (Byetta; 12.7). One percent of patients treated with exenatide extended-release (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 postmarketing with exenatide extended-release (Bydureon) use.

In clinical trials, injection site reaction was reported in 10.5 percent of patients on albiglutide (Tanzeum) compared to 2.1 percent on placebo.

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

## SPECIAL POPULATIONS<sup>109,110,111,112,113,114,115,116,117,118,119,120,121,122,123</sup>

### Pediatrics

No data are available for use of these agents in pediatric populations.

### Pregnancy

Albiglutide (Tanzeum), alogliptin (Nesina), alogliptin/metformin (Kazano), dulaglutide (Trulicity), sitagliptin (Januvia), sitagliptin/metformin (Janumet), sitagliptin/metformin ER (Janumet XR), saxagliptin (Onglyza), linagliptin (Tradjenta), linagliptin/metformin (Jentaducto), and saxagliptin/metformin ER (Kombiglyze XR) are Pregnancy Category B. Alogliptin/pioglitazone (Oseni), exenatide (Byetta, Bydureon), liraglutide (Victoza), and pramlintide (Symlin) are Pregnancy Category C.

### Renal Insufficiency

Metformin containing products, alogliptin/metformin (Kazano), linagliptin/metformin (Jentaducto), saxagliptin/metformin ER (Kombiglyze XR) and sitagliptin/metformin (Janumet, Janumet XR) in this review are contraindicated in patients with renal impairment (e.g., serum creatinine levels greater than

or equal to 1.5 mg/dL for men, greater than or equal to 1.4 mg/dL for women or abnormal creatinine clearance), since metformin can increase the risk of lactic acidosis.

Exenatide is not recommended for use in patients with a creatinine clearance (CrCl) less than 30 mL/min or end-stage renal disease.

Use **albiglutide, dulaglutide** and liraglutide with caution in this population, no dosage adjustment needed.

Linagliptin is nonrenally excreted; therefore no dosage adjustment is necessary in this population.

Renal function should be assessed prior to initiating therapy with sitagliptin and periodically during treatment. In patients with moderate renal impairment (CrCl 30 mL/min to 50 mL/min), the recommended daily dose of sitagliptin is 50 mg. In patients with severe renal impairment or end-stage renal disease on dialysis, the recommended daily dose of sitagliptin is 25 mg.

No dose adjustments for saxagliptin (Onglyza) are necessary for patients with mild renal impairment, but patients with moderate to severe renal impairment and end-stage renal disease requiring hemodialysis should receive saxagliptin 2.5 mg once daily. Saxagliptin is removed by hemodialysis.

### **Hepatic Insufficiency**

No dosage adjustment of **albiglutide (Tanzeum)**, exenatide (Byetta), exenatide extended-release (Bydureon), liraglutide (Victoza), linagliptin, or saxagliptin (Onglyza) is recommended for patients with hepatic 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.

Alogliptin/metformin, linagliptin/metformin, saxagliptin/metformin ER, sitagliptin/metformin, and sitagliptin/metformin ER use should be avoided in patients with hepatic disease.

### **Elderly**

Use alogliptin/metformin (Kazano), linagliptin/metformin (Jentadueto), saxagliptin/metformin ER (Kombiglyze XR), sitagliptin/metformin (Janumet), sitagliptin/metformin ER (Janumet XR), exenatide (Byetta), and exenatide extended-release (Bydureon) with caution as age increases and carefully monitor renal function. Do not use linagliptin/metformin (Jentadueto) in patients  $\geq 80$  years old unless normal renal function has been documented.

## DOSAGES

Drug	Dosing	Time of administration related to mealtime	Availability
<b>Amylin Analogue</b>			
pramlintide (Symlin) <sup>124</sup>	type 1 diabetes: initiate at 15 mcg SC injection, titrate to 30 or 60 mcg by 15 mcg increments	Prior to major meals, concurrently with insulin; decrease insulin doses 50 percent initially, then adjust only after reaching the target dose of pramlintide	1.5, 2.7 mL pens (1 mg/mL)
	type 2 diabetes: initiate at 60 mcg SC injection, titrate to 120 mcg as tolerated		
<b>DPP-4 Enzyme Inhibitors</b>			
alogliptin (Nesina®) <sup>125</sup>	25 mg once daily	Administer without regards to food	6.25 mg, 12.5 mg, 25 mg
alogliptin/metformin (Kazano®) <sup>126</sup>	One tablet twice daily; Adjust dose based on effectiveness and tolerability; Do not exceed 25 mg/2000 mg per day.	Administer with food	12.5 mg/500 mg, 12.5 mg/1000 mg tablets
alogliptin/ pioglitazone (Oseni®) <sup>127</sup>	One tablet once daily; Do not exceed 25 mg/45 mg per day	Administer without regards to food	12.5 mg/15 mg, 12.5 mg/30 mg, 12.5 mg/45 mg, 25 mg/15 mg, 25 mg/30 mg, 25 mg/45 mg tablets
linagliptin (Tradjenta) <sup>128</sup>	5 mg once daily	Take with or without food	5 mg tablet
linagliptin/metformin (Jentadueto™)	Starting dose 2.5 mg linagliptin/500 mg metformin twice daily for patients not already taking metformin. Or 2.5 mg linagliptin and current dose of metformin. May be increased gradually to 2.5 mg linagliptin/1,000 mg metformin 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 mg/500 mg 2.5 mg/850 mg; and 2.5 mg/1,000 mg Tablets
saxagliptin (Onglyza) <sup>129</sup>	2.5 to 5 mg daily by mouth	Take with or without food	2.5, 5 mg tablets
saxagliptin/ metformin ER (Kombiglyze XR) <sup>130</sup>	one tablet daily by mouth maximum per day: 5 mg saxagliptin, 2,000 mg metformin	Take with evening meal	5 mg/ 500 mg 5 mg/1,000 mg 2.5 mg/1,000 mg tablets

**Dosages (continued)**

Drug	Dosing	Time of administration related to mealtime	Availability
<b>DPP-4 Enzyme Inhibitors (continued)</b>			
sitagliptin (Januvia) <sup>131</sup>	100 mg once daily by mouth	Take with or without food	25, 50, 100 mg tablets
sitagliptin/ metformin (Janumet) <sup>132</sup>	one 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 mg/500 mg, 50 mg/1,000 mg tablets
sitagliptin/ metformin ER (Janumet XR) <sup>133</sup>	Dosage based on patient's current sitagliptin and/or metformin regimens up to a maximum of 1,000 mg metformin daily. In patients not currently on metformin: 100 mg sitagliptin and 1,000 mg metformin per day. maximum per day: 100 mg sitagliptin, 2,000 mg metformin	Once daily with a meal preferably in the evening Do not split, break, crush, or chew tablets	50 mg/500 mg 50 mg/1,000 mg 100 mg/1,000 mg tablets
<b>GLP-1 Receptor Agonists</b>			
albiglutide (Tanzeum) <sup>134</sup>	30 mg SC injection once weekly; may increase to 50 mg once weekly as needed for glycemic control	Administer at any time of day without regard to meals Administer on the same day each week	30 mg and 50 mg single-dose pen
dulaglutide (Trulicity) <sup>135</sup>	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 pen 0.75 mg/0.5 mL and 1.5 mg/0.5 mL single-dose prefilled syringe
exenatide (Byetta) <sup>136</sup>	5 mcg SC injection twice daily; dose can be increased to 10 mcg twice daily after one month	Administer at any time within the 60-minute period before the morning and evening meals preferably at least 6 hours apart	1.2, 2.4 mL prefilled pen containing 250 mcg/mL solution
exenatide extended-release (Bydureon) <sup>137</sup>	2 mg SC injection administered once weekly	Administer at any time without regard to meals	2 mg vial containing powdered exenatide with a 0.65 mL prefilled syringe containing diluents* 2 mg single-dose pen

**Dosages (continued)**

Drug	Dosing	Time of administration related to mealtime	Availability
liraglutide (Victoza) <sup>138</sup>	0.6 mg once daily SC injection into the upper arm, thigh or abdomen for one week. Dose may be increased to 1.2 mg once daily SC injection. Maximum dose is 1.8 mg daily.	Administer once daily at any time of day independent of meals Injection site and timing can be changed without dose adjustment	prefilled multidose pens that deliver 0.6 mg, 1.2 mg, and 1.8 mg doses. Pens contain 6 mg/mL (3 mL)

\* Prior to first use, exenatide (Byetta) and liraglutide (Victoza) must be stored refrigerated at 36°F to 46°F. After first use each product can be kept at a temperature not to exceed 77°F, if needed.

\* Exenatide extended-release (Bydureon) must be stored in the refrigerator up to the expiration date or until preparing for use. Each single use tray may be kept at room temperature not to exceed 77°F for no more than a total of four weeks, if needed.

Patients with moderate to severe renal impairment (CrCl ≤ 50 mL/min), end-stage renal disease, 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.<sup>139</sup>

Adjust pramlintide (Symlin) doses when there has been no clinically significant nausea for at least three 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.

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

Doses of **albiglutide (Tanzeum)**, **dulaglutide (Trulicity)**, exenatide (Byetta, Bydureon) and liraglutide (Victoza) should be injected in the thigh, abdomen, or upper arm, rotating sites regularly.

Initiating exenatide (Byetta) therapy at 5 mcg dosage reduces the incidence and severity of gastrointestinal side effects.

Gradually increase the dose of alogliptin/metformin, saxagliptin/metformin ER (Kombiglyze XR), sitagliptin/metformin (Janumet), or sitagliptin/metformin ER (Janumet XR) to reduce the gastrointestinal side effects of metformin.

Prior treatment with exenatide (Byetta) is not required when initiating exenatide extended-release (Bydureon) therapy. Patients changing from exenatide (Byetta) to exenatide extended-release (Bydureon) may experience transient (approximately two weeks) elevations in blood glucose concentrations.

When **albiglutide (Tanzeum)**, **dulaglutide (Trulicity)**, exenatide (Byetta, Bydureon), liraglutide (Victoza), saxagliptin (Onglyza) or saxagliptin/metformin (Kombiglyze XR) are used in combination with an insulin secretagogue (e.g., sulfonylurea) or with insulin, a lower dose of the insulin secretagogue or insulin may be required to minimize risk of hypoglycemia.

Sitagliptin/metformin ER, saxagliptin/metformin ER, alogliptin/metformin, and alogliptin/pioglitazone tablets should be swallowed whole and never crushed, cut, or chewed.

In patients already treated with metformin, the recommended starting dose of sitagliptin/metformin (Janumet XR) is sitagliptin 100 mg with the previously prescribed dosage of metformin. For those taking 850 mg or 1,000 mg of metformin twice daily, the starting dosage of the combined agent is two 50 mg sitagliptin/1,000 mg metformin ER tablets taken together once daily. If changing from sitagliptin/metformin immediate-release (Janumet) to sitagliptin/metformin extended-release (Janumet XR), maintain the same total daily dose of the individual components. For those with inadequate glycemic control, metformin may be gradually increased to the maximum of 2,000 mg daily.

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  $\geq 30$  to  $< 60$  mL/min) recommended dosage of alogliptin component is 12.5 mg daily in alogliptin-containing products (Nesina, Oseni).

## 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 percent 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/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.

### Amylin Analogues

#### *pramlintide (Symlin)*

In a double-blind, placebo-controlled, parallel-group, multicenter study, 651 patients with type 1 diabetes were randomized to mealtime injections of placebo or pramlintide in addition to insulin therapy for 52 weeks.<sup>140</sup> Addition of pramlintide 60 mcg three or four times daily to insulin resulted in significant reductions in HbA1c from baseline of 0.29 percent ( $p < 0.011$ ) and 0.34 percent ( $p < 0.001$ ), respectively, compared to a 0.04 percent 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 type 1 diabetes to pramlintide or placebo as an adjunct to insulin.<sup>141</sup> Insulin use was adjusted as needed. Baseline HbA1c was 8.1 percent for both groups. At week 29, HbA1c reductions were similar for both study arms (both -0.5 percent). Pramlintide treatment significantly reduced postprandial glucose excursions (p<0.0005) and weight (pramlintide -1.3 ± 0.30 kg; placebo +1.2 ± 0.30 kg; p<0.0001). At week 29, insulin dose decreased by 28 and 4 percent in pramlintide- and placebo-treated groups, respectively. Nausea was reported by 63 and 36 percent 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 type 2 diabetes treated with insulin alone or in combination with sulfonylureas and/or metformin were randomized to receive additional preprandial injections of either placebo or pramlintide.<sup>142</sup> 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 percent at weeks 26 and 52, respectively), compared to placebo (p<0.05). The percentage of patients achieving HbA1c <8 percent was 46 percent for the pramlintide group and 28 percent 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)***

A double-blind, placebo-controlled study was conducted over 26 weeks in patients (n=329) with type 2 diabetes.<sup>143,144</sup> Patients were randomized to receive alogliptin 12.5 mg, 25 mg, or placebo once daily. Baseline characteristics were similar among the groups. Statistically significant improvements in baseline HbA1c occurred in patients taking alogliptin 12.5 mg and 25 mg daily compared to patients taking placebo (-0.56, -0.59 percent versus -0.02, respectively; 95% CI, p<0.01) as early as Week-4. Significantly greater reductions in fasting plasma glucose (FPG) were found with alogliptin 12.5 mg and 25 mg compared to placebo (-10.6 mg/dL, -16.4 mg/dL, and +11.3 mg/dL, respectively; p<0.001). The proportion of patients achieving an HbA1c level of less than or equal to seven percent were 47.4 percent, 44 percent and 23 percent for alogliptin 12.5 mg, 25 mg and placebo patients, respectively (p<0.01). The mean change in body weight with alogliptin was similar to placebo.

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

A total of 655 patients with a mean baseline HbA1c of 8.8 percent 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.<sup>145,146</sup> Mean baseline HbA1c and 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 percent of patients achieving an HbA1c of less than or equal to seven percent was 24 percent, 34 percent, 53 percent and 63 percent 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 percent were randomized to one of seven 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.<sup>147</sup> 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 percent of patients achieving an HbA1c less than seven percent was four percent, 20 percent, 27 percent, 34 percent, 47 percent, and 59 percent 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 type 2 diabetes 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.<sup>148</sup> 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 percent and eight percent 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 seven percent was 44 percent and 18 percent 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 type 2 diabetes already on metformin at doses of at least 1,500 mg per day or at maximum tolerated dose were randomized to one 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.<sup>149</sup> Patients treated with Nesina with pioglitazone had statistically significant improvements in A1c and FPG compared to patients treated with placebo, Nesina alone, or pioglitazone alone when added to background metformin treatment (95% CI,  $p \leq 0.01$ ). The percent of patients achieving an HbA1c of less than or equal to seven percent was six percent, 27 percent, 26 percent, 30 percent, 36 percent, 55

percent, 53 percent, and 60 percent 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 ( $p \leq 0.01$ ). The mean change from baseline in FPG was seven 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 type 2 diabetes 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.<sup>150</sup> Patients were maintained on a stable dose of metformin (median dose equal to 1,700 mg). Prior to randomization patients underwent a four-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 seven percent was 33 percent (alogliptin 25 mg with pioglitazone 30 mg and metformin) and 21 percent (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 four 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 type 2 diabetes who were insufficiently controlled on a thiazolidinedione alone or in combination with a sulfonylurea or metformin.<sup>151</sup> Prior to randomization patients underwent a four-week single-blind, placebo run-in period. Patients had a mean baseline HbA1c of eight percent 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 equals 30 mg). Patients who were previously treated with metformin (median dose equals 2,000 mg) or sulfonylurea (median dose equals ten 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 percent of patients achieving an HbA1c of less than or equal to seven percent was 49 percent (alogliptin 25 mg with pioglitazone with or without metformin or a sulfonylurea) and 34 percent (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 negative six mg/dL (placebo with pioglitazone with or without metformin or a sulfonylurea).

#### ***linagliptin (Tradjenta)***

In two double-blind, multicenter trials ( $n > 350$  evaluable patients/trial) in adult patients with inadequately controlled type 2 diabetes mellitus, 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 percent to -0.88 percent 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.<sup>152</sup>

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 was conducted to examine the efficacy and safety of the DPP-4 inhibitor linagliptin in persons with Type 2 diabetes mellitus inadequately controlled (HbA1c = 7 to 10) by metformin plus sulfonylurea. At week 24 the linagliptin placebo-corrected HbA1c adjusted mean change from baseline was -0.62 percent ( $p < 0.0001$ ). More participants with baseline HbA1c > 7 achieved an HbA1c < 7 with linagliptin (29.2 percent) compared with placebo (8.1 percent,  $p < 0.0001$ ). Fasting plasma glucose was reduced with linagliptin relative to placebo (-0.7 mmol/L, 95% CI -1 to -0.4;  $p < 0.0001$ ). Improvements in homeostasis model assessment of  $\beta$ -cell function were seen with linagliptin ( $p < 0.001$ ). The proportion of patients who reported a severe adverse event was low in both groups (linagliptin 2.4 percent, placebo 1.5 percent). Symptomatic hypoglycemia occurred in 16.7 and 10.3 percent of the linagliptin and placebo groups, respectively. Hypoglycemia was generally mild or moderate; severe hypoglycemia was reported in 2.7 and 4.8 percent of the participants experiencing hypoglycemic episodes in the linagliptin and placebo arms, respectively. No significant weight changes were noted. It was concluded that adding linagliptin to metformin in combination with a sulfonylurea significantly improved glycemic control in patients with Type 2 diabetes and was well tolerated.<sup>153</sup>

In a 24-week study, patients with type 2 diabetes were randomized to receive the initial combination of 30 mg pioglitazone plus 5 mg linagliptin ( $n=259$ ) or pioglitazone plus placebo ( $n=130$ ).<sup>154</sup> The primary endpoint of change from baseline in HbA1c with the initial combination of linagliptin plus pioglitazone was -1.06 percent compared with -0.56 percent for placebo plus pioglitazone (95% CI -0.71, -0.3;  $p < 0.0001$ ). Reductions in fasting plasma glucose (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 of < 7 percent (42.9 versus 30.5 percent, respectively;  $p=0.0051$ ) and reduction in HbA1c of  $\geq 0.5$  percent (75 versus 50.8 percent, respectively;  $p < 0.0001$ ). Hypoglycemic episodes, all mild in severity, occurred in 1.2 percent of the linagliptin plus pioglitazone patients and none in the placebo plus pioglitazone group.

In a phase III, double-blind, placebo-controlled trial, patients with inadequately controlled type 2 diabetes mellitus on sulfonylurea monotherapy were randomly assigned to receive treatment with linagliptin 5 mg once or placebo as adjunctive therapy to sulfonylurea therapy.<sup>155</sup> 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 percent ( $p < 0.0001$ ). Patients in the linagliptin group were more likely to achieve the HbA1c target level of <7 percent after 18 weeks of treatment (15.2 percent versus 3.7 percent, 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 hypoglycemic, 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/metformin (Jentadueto)**

There have been no clinical efficacy studies performed with linagliptin/metformin (Jentadueto). However, coadministration of the single entity medications has been studied in type 2 diabetes mellitus patients who were not well controlled in their diet and exercise and in combination with a sulfonyleurea. The bioequivalence of Jentadueto 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.<sup>156</sup> Patients (52 percent) entering the study already on antihyperglycemic therapy went through a four week wash out period followed by a two week placebo run-in period. Patients who had inadequate glycemic control (HbA1c greater than or equal to seven percent and less and or equal to 10.5 percent) were randomized into the study. Forty-eight percent of patients entering the study were not taking an antihyperglycemic and went straight into the two week placebo run-in phase. Patients who had inadequate glycemic control (HbA1c greater than or equal to 7.5 percent and less 11 percent) after the two week placebo run-in phase were randomized into the study. Randomization was stratified by baseline HbA1c (less than 8.5 percent versus greater than or equal to 8.5 percent) and prior use of an antihyperglycemic medication. Patients were randomized in a 1:2:2:2:2 ratio to either placebo or one of the five 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 percent. The fasting plasma glucose 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 percent and p<0.0001.

A 24-week, double-blind, randomized, placebo-controlled study was performed in 701 patients with type 2 diabetes to test the efficacy of adding linagliptin to metformin.<sup>157,158</sup> There were 491 patients taking metformin greater than or equal to 1,500 mg per day who entered the study after a two week run-in period with placebo. There were 207 patients taking metformin plus another oral antihyperglycemic who entered the study after stopping the other oral antihyperglycemic and performing a run-in phase with metformin monotherapy of at least 1,500 mg per day. Patients were then randomized to the addition of linagliptin 5 mg or placebo once daily. If necessary, rescue glimepiride was administered to patients with poor glycemic control. When comparing the linagliptin plus metformin group to the placebo plus metformin group statistically significant improvements were seen in HbA1C (-0.5 percent versus 0.15 percent), fasting plasma glucose (-11 mg/dL and 11mg/dL), and 2-hour postprandial glucose levels (-49 mg/dL versus 18 mg/dL) for those treated with linagliptin (CI 95%). Rescue glimepiride therapy was needed in 7.8 percent of patients using linagliptin plus metformin versus 18.9 percent using placebo plus metformin (CI 95%). Overall, 28.3 percent of the

linagliptin plus metformin group and 11.4 percent of the placebo plus metformin group reached an HbA1c goal of less than seven percent (CI 95%).

A 104-week double-blind, glimepiride-controlled, non-inferiority study was performed in patients with type 2 diabetes with insufficient glycemic control despite being on metformin compared to patients having coadministration of linagliptin plus metformin.<sup>159</sup> Patients on metformin monotherapy had a run-in period of two weeks and patients taking metformin with another oral antihyperglycemic had a metformin monotherapy (daily dose at least 1,500 mg) run-in period of six weeks and washout of the other antihyperglycemic agent. After an additional two week placebo run-in period patients with poor glycemic control (HbA1c 6.5 to 10 percent) 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 fasting plasma glucose levels, -0.4 percent and -0.6 percent (CI 97.5 percent) 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 percent, 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 type 2 diabetes 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. The study determined that linagliptin provided statistically significant improvements in HbA1c and fasting plasma glucose levels. Patients treated with linagliptin plus metformin and a sulfonylurea had a reduction in HbA1c and fasting plasma glucose levels, -0.7 percent and -5 mg/dL, respectively, and patients using placebo plus metformin and a sulfonylurea had a reduction of -0.1 percent in HbA1c levels but an increase of 8 mg/dL in fasting plasma glucose levels (CI 95%). Rescue therapy was needed in 5.4 percent of patients treated in the linagliptin group versus 13 percent in the placebo group. Overall, 31.2 percent of the linagliptin plus metformin and sulfonylurea patients and 9.2 percent of the placebo plus metformin and sulfonylurea patients reached a goal HbA1c level of less than seven percent.<sup>160</sup>

### **saxagliptin (Onglyza)**

The efficacy and safety of once-daily saxagliptin monotherapy were evaluated in treatment-naïve patients with type 2 diabetes and inadequate glycemic control for 24 weeks.<sup>161</sup> The study enrolled 401 patients with HbA1c of seven to 10 percent. These patients were randomized and treated with oral saxagliptin 2.5, 5, 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 fasting plasma glucose (FPG), proportion of patients achieving HbA1c < 7 percent, and changes in postprandial glucose area-under-the-curve (PPG-AUC). Results demonstrated that saxagliptin significantly decreased HbA1c by -0.43 percent, -0.46 percent, -0.54 percent for saxagliptin 2.5, 5, and 10 mg, respectively, versus +0.19 percent 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, 5, 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 percent was achieved by week 24 in 35 percent (p=NS), 38 percent (p=0.0443), 41 percent (p=0.0133) for

saxagliptin 2.5 mg, 5 mg, and 10 mg groups where as placebo rate was 24 percent. 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  $\leq 50$  mg/dL) were observed. Saxagliptin was not associated with weight gain.

A randomized, 24-week, phase III, double-blind trial evaluated the efficacy and safety of saxagliptin added to a submaximal sulfonylurea dose in comparison to uptitration of sulfonylurea monotherapy in patients with type 2 diabetes taking sulfonylurea monotherapy with inadequate glycemic control.<sup>162</sup> Initially, all patients received open-label glyburide 7.5 mg daily for four weeks. A total of 768 patients between 18 to 77 years of age with HbA1c screening value of 7.5 to 10 percent 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 uptitration glyburide was allowed in the glyburide-only arm to a maximum total daily dose of 15 mg. Results at 24 weeks indicated that 92 percent of glyburide-only patients were uptitrated 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 uptitrated glyburide in HbA1c (-0.54 percent, -0.64 percent versus +0.08 percent, 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 percent was greater for saxagliptin 2.5 and 5 mg versus uptitrated glyburide (22.4 percent and 22.8 percent versus 9.1 percent, respectively; both  $p<0.0001$ ). Postprandial glucose area under the curve was reduced for saxagliptin 2.5 and 5 mg versus uptitrated 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 uptitrated glyburide (13.3 percent and 14.6 percent versus 10.1 percent, respectively).

A multicenter, randomized, double-blind, active-controlled, phase III 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.<sup>163</sup> Patients enrolled in the study were 18 to 77 years old, had HbA1c 8 to 12 percent, fasting C-peptide concentration  $\geq 1$  ng/mL, and body mass index  $\leq 40$  kg/m<sup>2</sup>. 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 five 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 percent, 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 percent versus -1.7 and -2 percent, all  $p<0.0001$  versus monotherapy) and FPG (-60 and -62 mg/dL versus -31 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 percent 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 type 2 diabetes.<sup>164</sup> Seven-hundred forty-three patients with inadequate glycemic control on metformin monotherapy and HbA1c > 7 percent and < 10 percent were randomly assigned to either saxagliptin at three different doses (2.5, 5, 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), percent of patients achieving HbA1c <7 percent, 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, 5, and 10 mg groups were -0.59, -0.69, and -0.58 percent versus placebo group reporting HbA1c +0.13 percent. The percentages of patients achieving HbA1c of <7 percent were 37, 44, and 44 percent for the saxagliptin 2.5, 5 and 10 mg groups compared to 17 percent for placebo (all  $p < 0.0001$ ). Incidence of hypoglycemic adverse events and weight reductions were similar between the two groups.

The efficacy and safety of saxagliptin plus TZD in 565 patients with type 2 diabetes and inadequate glycemic control on TZD monotherapy were evaluated in a multicenter, randomized, double-blind, phase III study.<sup>165</sup> Patients had a baseline HbA1c of 7 to 10.5 percent while on pioglitazone 30 or 45 mg or rosiglitazone 4 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 percent ( $p = 0.0007$ ) for saxagliptin 2.5 mg and -0.94 percent ( $p < 0.0001$ ) for saxagliptin 5 mg compared to -0.3 percent with placebo. The percentage of patients achieving HbA1c <7 percent was 42.2 ( $p = 0.001$ ), 41.8 ( $p = 0.0013$ ), and 25.6 percent for saxagliptin 2.5 plus TZD, 5 mg plus TZD, and placebo groups, respectively. Hypoglycemic events were similar across all groups.

A total of 455 patients with type 2 diabetes 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  $\geq 7.5\%$  and  $\leq 11\%$ ) on insulin alone ( $n = 141$ ) or on insulin in combination with a stable dose of metformin ( $n = 314$ ).<sup>166</sup> 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, four-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 percent versus -0.3 percent for placebo (-0.4 percent adjusted mean difference from placebo,  $p < 0.0001$ ). Add-on therapy with saxagliptin also resulted in a significant two-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 percent for saxagliptin versus 32 percent for placebo. In the saxagliptin group, the overall incidence of reported hypoglycemia was 18.4 percent versus 19.9 percent for placebo. However, the incidence of confirmed symptomatic hypoglycemia (finger stick blood glucose  $\leq 50$  mg/dL) was higher with saxagliptin at 5.3 percent versus placebo at 3.3 percent.

A total of 257 patients with type 2 diabetes participated in a 24-week, randomized double-blind, placebo-controlled trial.<sup>167</sup> Patients were to be on a stable combined dose of metformin extended-

release 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  $\geq 50$  percent of the maximum recommended dose) for at least eight 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 A1C 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 five percent in the placebo group. The change in fasting plasma glucose from baseline to Week 24 was not statistically significant. The percent of patients achieving an A1C  $< 7$  percent was 31 percent add-on saxagliptin compared to nine percent with add-on placebo. Significance was not tested. The overall incidence of reported hypoglycemia was 10.1 percent for the saxagliptin group and 6.3 percent for the placebo group. The overall incidence of reported hypoglycemia was 10.1 percent for saxagliptin 5 mg and 6.3 percent for placebo. Confirmed hypoglycemia was reported in 1.6 percent of patients treated with saxagliptin and in none of the patients treated with placebo.

### ***saxagliptin/metformin extended-release (Kombiglyze XR)***

No large scale clinical efficacy or safety studies have been conducted specifically with saxagliptin and metformin extended-release. FDA approved once-daily saxagliptin and metformin ER based upon two phase III 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.

A 24-week randomized, double-blind, active-controlled trial evaluated the efficacy and safety of saxagliptin coadministered with metformin IR in 1,306 treatment-naïve patients with inadequate glycemic control (HbA1c  $\geq 8$  to  $\leq 12$  percent) on diet and exercise alone.<sup>168</sup> After a single-blind, one-week, dietary and exercise placebo lead-in period, patients were randomized to one of four treatment arms: saxagliptin 5 mg/metformin IR 500 mg, saxagliptin 10 mg/metformin IR 500 mg, saxagliptin 10 mg/placebo, or metformin IR 500 mg/placebo. Saxagliptin was dosed once daily. In the three treatment groups using metformin IR, the metformin dose was up-titrated weekly in 500 mg per day increments, as tolerated, to a maximum of 2,000 mg per day based on fasting plasma glucose (FPG). Patients who failed to meet specific glycemic goals during this study were treated with pioglitazone rescue as add-on therapy. Coadministration of saxagliptin 5 mg plus metformin IR provided significant improvements in HbA1c (-2.5 versus -2), FPG (-6 versus -4.7), and post-prandial glucose (PPG; -138 versus -97) compared with placebo plus metformin IR. The maximum recommended approved saxagliptin dose is 5 mg daily; the 10 mg daily dose of saxagliptin does not provide greater efficacy than the 5 mg daily dose.

A total of 743 patients with type 2 diabetes mellitus with inadequate glycemic control (HbA1c  $\geq 7$  and  $\leq 10$  percent) on metformin (1,500-2,000 mg per day for at least eight weeks) alone participated in a 24-week, randomized, double-blind, placebo-controlled trial.<sup>169</sup> During a single-blind, two-week, dietary and exercise placebo lead-in period, patients received metformin IR at their pre-study dose, up to 2,500 mg daily, for the duration of the study. Patients were then randomized to saxagliptin 2.5 mg, 5 mg, or 10 mg or placebo in addition to their current dose of open-label metformin IR. Patients who failed to meet specific glycemic goals during the study received pioglitazone rescue therapy. Dose

titrations of saxagliptin and metformin IR were not permitted. Saxagliptin 2.5 mg and 5 mg add-on to metformin IR provided significant improvements in HbA1c (-0.6, -0.7, +0.1, respectively), FPG (-14, -22, +1, respectively), and PPG (-66, -58, -18, respectively) compared with placebo add-on to metformin IR. The maximum recommended approved saxagliptin dose is 5 mg daily; 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 type 2 diabetes who were on metformin and evaluated for 24 weeks.<sup>170</sup> Patients had a baseline HbA1c of  $\geq 7$  percent to  $\leq 10$  percent (baseline of 8 percent) and 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 percent by sitagliptin. Significantly more patients on sitagliptin (47 percent) achieved HbA1c of  $< 7$  percent compared to placebo (18.3 percent). 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.<sup>171</sup>

### ***sitagliptin (Januvia), sitagliptin/metformin (Janumet) and sitagliptin/metformin ER (Janumet XR)***

The co-administration of sitagliptin and metformin immediate-release has been studied in patients with type 2 diabetes inadequately controlled on diet and exercise and in combination with other antidiabetic medications.

There have been no clinical efficacy or safety studies conducted with sitagliptin/metformin (Janumet), or sitagliptin/metformin ER (Janumet XR) to characterize effect on hemoglobin A1c (HbA1C) reduction. Bioequivalence of Janumet to co-administered sitagliptin and metformin immediate-release tablets and of Janumet XR tablet to co-administered sitagliptin and extended-release metformin tablets has been demonstrated.

In a 24-week, double-blind, placebo-controlled, parallel-group study, 1,091 patients with type 2 diabetes and HbA1c 7.5 to 11 percent 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.<sup>172</sup> Patients who had an HbA1c  $> 11$  percent or a fasting glucose value  $> 280$  mg/dl after the run-in period were not eligible to be randomized. The mean baseline HbA1c was 8.8 percent. The placebo-subtracted HbA1c changes from baseline were -2.07 percent (sitagliptin/metformin 2,000 mg), -1.57 percent (sitagliptin/metformin 1,000 mg), -1.30 percent (metformin 2,000 mg), -0.99 percent (metformin 1,000 mg), and -0.83 percent (sitagliptin 100 mg) ( $p < 0.001$  for comparisons versus placebo and for coadministration versus respective monotherapies). The percentage of patients achieving HbA1c  $< 7$  percent was 66 percent 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 percent) across active treatment groups and not significantly different from that in the placebo group (0.6 percent).

### ***sitagliptin (Januvia) and saxagliptin (Onglyza)***

Adult patients with type 2 diabetes ( $n = 801$ ) and an HbA1c of 6.5 to 10 percent 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.<sup>173</sup> The adjusted mean changes in HbA1c following the addition of saxagliptin or

sitagliptin to stable metformin therapy were -0.52 and -0.62 percent, respectively. The between-group difference was 0.09 percent (95% CI, - 0.01 to 0.20 percent), demonstrating noninferiority as defined as an upper limit of the two-sided 95% CI of the HbA1c difference between treatments was <0.3 percent). Both treatments were generally well tolerated; incidence and types of adverse events were comparable between groups. Hypoglycemic events, mostly mild, were reported in approximately three percent of patients in each treatment group. Body weight declined by a mean of 0.4 kg in both groups.

### ***sitagliptin (Januvia) and 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.<sup>174</sup> From a mean baseline HbA1c of 7.5 percent, changes from baseline were -0.67 percent at week 52 in both groups, confirming noninferiority. The proportions of patients achieving an HbA1c <7 percent were 63 percent (for sitagliptin) and 59 percent (for glipizide). The proportion of patients experiencing hypoglycemia was significantly higher with glipizide than with sitagliptin (32 versus 5 percent; 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) and 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.<sup>175</sup> 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 percent baseline: -0.73 percent for sitagliptin (p<0.001 versus placebo) and -0.79 percent for rosiglitazone compared with -0.22 percent 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 percent was 55 percent with sitagliptin, 63 percent with rosiglitazone and 38 percent 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 greater than 3 kg increase in body weight was 21 percent in the rosiglitazone group compared with two percent 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.

The efficacy and tolerability of sitagliptin added to pioglitazone (Actos®) therapy were assessed in patients with type 2 diabetes and HbA1c >7 percent and <10 percent while receiving a stable dose of pioglitazone of 30 to 45 mg per day.<sup>176</sup> 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 end point was change from baseline in HbA1c at week 24. Mean baseline HbA1c was 8.1 percent in the sitagliptin group and 8 percent in the placebo group. After 24 weeks, sitagliptin added to pioglitazone therapy was associated with significant reductions in HbA1c (-0.70 percent; 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 percent and 7.8 percent in the sitagliptin and placebo groups, respectively, and the proportions of patients reaching a target HbA1c of <7 percent

were 45.4 and 23 percent, respectively ( $p < 0.001$ ). Sitagliptin was generally well tolerated, with no increased risk of hypoglycemia compared with placebo.

### ***sitagliptin/metformin (Janumet) and metformin***

In a 24-week, randomized, double-blind, placebo-controlled study, 701 patients with type 2 diabetes participated to compare sitagliptin/metformin to metformin alone.<sup>177,178</sup> Patients already on metformin 1,500 mg per day or higher ( $n=431$ ) were randomized after completing a two-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 eight weeks,  $n=41$ ) were randomized after a run-in period of approximately ten 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 percent in both groups. HbA1c changes from baseline were -0.7 percent for sitagliptin/metformin and zero percent for placebo/metformin. The percentage of patients achieving a HbA1c  $< 7$  percent was 47 in the sitagliptin/metformin immediate-release group compared to 18 percent in the metformin immediate-release monotherapy group.

### ***sitagliptin/metformin/rosiglitazone (Janumet/rosiglitazone) and metformin/rosiglitazone***

In a randomized, double-blind, placebo-controlled study, 278 patients with type 2 diabetes participated in a comparison of sitagliptin in combination with metformin and rosiglitazone.<sup>179,180</sup> Patients on dual therapy with metformin  $\geq 1,500$  mg/day and rosiglitazone  $\geq 4$  mg/day or with metformin  $\geq 1,500$  mg/day and pioglitazone  $\geq 30$  mg/day (switched to rosiglitazone  $\geq 4$  mg/day) entered a dose-stable run-in period of six weeks. Patients on other dual therapy were switched to metformin  $\geq 1,500$  mg/day and rosiglitazone  $\geq 4$  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 percent to 11 percent) 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 percent for patients treated with sitagliptin and -0.3 percent for patients treated with placebo.

## **GLP-1 Agonists**

### ***albiglutide (Tanzeum)***

A 52-week, double-blind, placebo-controlled, trial evaluated monotherapy with albiglutide. A total of 296 type 2 diabetic patients inadequately controlled on diet and exercise were randomized (1:1:1) to albiglutide 30 mg subcutaneously (SC) weekly, albiglutide 30 mg SC weekly uptitrated to 50 mg SC weekly at Week 12, or placebo. Treatment with albiglutide 30 mg or 50 mg weekly resulted in statistically significant reductions in HbA1c from baseline at Week 52 compared to placebo. The adjusted mean change in weight from baseline did not differ significantly between albiglutide and placebo.

### ***albiglutide (Tanzeum) versus sitagliptin or glimepiride as add on to metformin***

A 104-week, randomized, double-blind, trial evaluated the efficacy of albiglutide in 999 patients with type 2 diabetes inadequately controlled on  $\geq 1,500$  mg daily of metformin. Albiglutide 30 mg SC weekly with optional uptitration to 50 mg SC weekly after at least four weeks was compared to placebo, sitagliptin 100 mg daily, or glimepiride 2 mg daily with optional uptitration to 4 mg daily. Treatment

with albiglutide as add-on to metformin resulted in statistically significant greater reductions in HbA1c from baseline at Week 104 compared to placebo, sitagliptin, and glimepiride as add-on to metformin. At week 104, the difference in body weight change from baseline between albiglutide and glimepiride was significant.

#### ***albiglutide (Tanzeum) plus pioglitazone (Actos)***

A 52-week, double-blind, trial evaluated the efficacy of albiglutide in 299 type 2 diabetic patients inadequately controlled on  $\geq 30$  mg daily of pioglitazone (with or without  $\geq 1,500$  mg daily of metformin). Patients were randomized to get albiglutide 30 mg SC weekly or placebo. Treatment with albiglutide as add-on to pioglitazone resulted in statistically significant HbA1c reduction from baseline at Week 52 compared to placebo as add-on to pioglitazone. There was no statistically significant difference in mean change from baseline in weight between albiglutide and placebo.

#### ***albiglutide (Tanzeum) versus pioglitazone as add-on to metformin plus sulfonylurea***

A 52-week, double-blind, trial evaluated the efficacy of albiglutide in 657 type 2 diabetic patients inadequately controlled on  $\geq 1,500$  mg daily of metformin and glimepiride 4 mg daily. Patients were randomized to receive albiglutide 30 mg SC weekly with optional uptitration to 50 mg weekly after at least four weeks, placebo, or pioglitazone 30 mg daily with optional uptitration to 45 mg per day. Compared to placebo, albiglutide treatment resulted in statistically significant HbA1c reductions from baseline. Against pioglitazone, albiglutide treatment did not meet pre-specified, non-inferiority margin (0.3 percent) [(Difference was 0.25 with CI=(0.10, 0.40)]. Albiglutide provided less reduction in HbA1c than pioglitazone and the treatment difference was statistically significant. Body weight change from baseline for albiglutide did not differ significantly from placebo but was significantly different when compared with pioglitazone.

#### ***albiglutide (Tanzeum) versus liraglutide (Victoza)***

A 32-week, randomized, open-label, liraglutide-controlled, non-inferiority trial evaluated the efficacy of albiglutide in 805 type 2 diabetic patients inadequately controlled on monotherapy or combination oral antidiabetic therapy (metformin, thiazolidinedione, sulfonylurea, or combination of these). Patients were randomized to albiglutide 30 mg SC weekly with uptitration to 50 mg weekly at Week-6 or liraglutide 1.8 mg daily titrated up from 0.6 mg at Week-1 and 1.2 mg at Week-1 to Week-2. Albiglutide did not meet the prespecified criteria for non-inferiority. Albiglutide provided less reduction in HbA1c than liraglutide and treatment difference was statistically significant.

#### ***albiglutide (Tanzeum) versus basal insulin glargine (Lantus®)***

A 52-week, randomized (2:1), open-label, insulin glargine-controlled, non-inferiority trial was used to evaluate the efficacy of albiglutide in 735 type 2 diabetic patients inadequately controlled on  $\geq 1,500$  mg daily of metformin (with or without sulfonylurea). Patients were randomized to receive albiglutide 30 mg SC weekly with optional uptitration to 50 mg SC weekly or insulin glargine initiated at 10 units/day and titrated weekly per prescribing information. Change in HbA1c from baseline compared to insulin glargine was the primary endpoint. The initial daily dose of insulin glargine ranged between 2 and 20 units (median of 10 units) and ranged between 3 and 230 units (median 30 units) at Week 52. Seventy-seven percent of the patients treated with albiglutide were uptitrated to 50 mg SC weekly. Albiglutide met the prespecified criteria for non-inferiority compared to insulin glargine. For

albiglutide, a mean decrease in body weight was observed compared to a mean increase in body weight for insulin glargine; the difference was statistically significant.

### ***albiglutide (Tanzeum) versus prandial insulin lispro (Humalog®)***

A 26-week, open-label, multicenter, non-inferiority trial was used to evaluate the efficacy of albiglutide in 563 type 2 diabetic patients inadequately controlled on insulin glargine. Patients were randomized to receive albiglutide 30 mg SC once weekly with uptitration to 50 mg SC weekly, if needed, after Week 8 or insulin lispro administered daily at meals and started according to standard of care and titrated to desired effect. The between-treatment difference of -0.2 percent between albiglutide and insulin lispro met the pre-specified non-inferiority criteria. A mean weight loss for albiglutide treatment resulted and a mean weight gain resulted for insulin lispro treatment. The difference between the groups was statistically significant.

### ***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 ( $HbA1c \geq 6.5\%$  and  $\leq 9.5\%$ ) with diet and exercise with or without one anti-diabetic agent used at submaximal dose.<sup>181,182</sup> 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  $\leq 6.5\%$  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 type 2 diabetes.<sup>183</sup> 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 type 2 diabetes not adequately controlled with metformin and pioglitazone.<sup>184,185</sup> Patients were randomized to dulaglutide 1.5 mg or 0.75 mg, exenatide 10 mcg twice daily, or placebo. Patients were also on metformin  $\geq 1,500$  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 type 2 diabetes 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 percent 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.<sup>186</sup> 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 three 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 type 2 diabetes who were also on metformin.<sup>187</sup> 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 non-inferiority of dulaglutide compared to liraglutide. No severe hypoglycemia was reported. Gastrointestinal adverse events were reported similarly in both treatment groups.

#### ***exenatide (Byetta)***

A triple-blind, placebo-controlled, multicenter, 30-week study evaluated exenatide in patients with type 2 diabetes who had inadequate treatment with sulfonylureas.<sup>188</sup> Average HbA1c was 8.6 percent at baseline, and were comparable across treatment arms. After a four-week, single-blind, placebo lead-in period, 377 subjects were randomized and began four 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 four weeks. All subjects continued sulfonylurea therapy. At week

30, HbA1c changes from baseline were -0.86, -0.46, and +0.12 percent in the exenatide 10 mcg, 5 mcg, and placebo arms, respectively (adjusted  $p < 0.001$ ). Of evaluable subjects with baseline HbA1c > 7 percent ( $n = 237$ ), 41 percent (exenatide 10 mcg), 33 percent (exenatide 5 mcg), and 9 percent (placebo) achieved HbA1c  $\leq 7$  percent ( $p < 0.001$ ). 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.<sup>189</sup> Some authors credited with the publications have been involved with manufacturer-funded studies of exenatide.

A double-blind, placebo-controlled study with 733 patients with type 2 diabetes and inadequate glycemic control with combined metformin-sulfonylurea therapy, found comparable results at 30 weeks using the same treatment arms as the above study.<sup>190</sup> At week 30, HbA1c changes from baseline were -0.8 percent (exenatide 10 mcg), -0.6 percent (exenatide 5 mcg), and +0.2 percent (placebo, adjusted  $p < 0.0001$  versus placebo). Placebo adjusted reductions were -1 percent for exenatide 10 mcg and -0.8 percent for exenatide 5 mcg groups. In the evaluable population, exenatide-treated patients were more likely to achieve HbA1c  $\leq 7$  percent than placebo-treated patients (34 percent, exenatide 10 mcg group; 27 percent, exenatide 5 mcg group; and nine percent, placebo;  $p < 0.0001$ ). Weight loss occurred in both exenatide treated groups (-1.6 kg,  $p \leq 0.01$  versus placebo). Mild or moderate nausea was the most frequently reported adverse event. Hypoglycemia was reported in 28 percent of exenatide 10 mcg group, 19 percent of exenatide 5 mcg group, and 13 percent of the placebo group.

#### ***exenatide extended-release (Bydureon) and exenatide (Byetta)***

DURATION-1<sup>191</sup>: A 30-week, randomized, open-label, non-inferiority study compared exenatide ER 2 mg administered once weekly to exenatide 10 mcg administered twice a day, in 295 patients with type 2 diabetes (HbA1c 8.3 percent, mean fasting plasma glucose 9 mmol/L, and weight 102 kg [SD 20]). The patients were naive to drug therapy, or on one 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 percent or less (77 percent once weekly exenatide versus 61 percent 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.<sup>192</sup> 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 extended-release.

DURATION-5<sup>193,194</sup>: 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 type 2 diabetes and inadequate glycemic control with diet and exercise alone or with oral antidiabetic therapy, including metformin, a sulfonylurea, a thiazolidinedione, or combination of two of those therapies. The mean baseline HbA1c was 8.4 percent. 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 percent of subjects treated with exenatide ER, respectively and 35, 4.1, and 2.4 percent of subjects treated with exenatide, respectively. No major incidence of hypoglycemia was reported.

***exenatide (Byetta) and insulin glargine (Lantus®)***

In a 30-week, double-blind, placebo-controlled trial, adults with type 2 diabetes and an HbA1c level of 7.1 to 10.5 percent 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.<sup>195</sup> At randomization, participants (n=261) with HbA1c levels greater than 8.0 percent continued to receive their current dose of insulin glargine; those with HbA1c  $\leq$  8.0 percent decreased their dose by 20 percent. Insulin glargine doses were maintained for five weeks, after which doses were titrated to achieve a fasting glucose level less than 100 mg/dL. The HbA1c level decreased by 1.74 percent in the exenatide group and by 1.04 percent in the placebo group ( $p < 0.001$ ). At 30 weeks, the proportion of participants that achieved HbA1c  $\leq$  7.0 percent was 60 percent in the exenatide group and 35 percent 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 one placebo patient discontinued due to adverse events ( $p < 0.010$ ).

In a 26-week multicenter, open-label, randomized, controlled trial, 551 patients with type 2 diabetes 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.<sup>196</sup> At week 26, both exenatide and insulin glargine reduced HbA1c levels by 1.11 percent. 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 percent), vomiting (17.4 versus 3.7 percent), and diarrhea (8.5 versus three percent) 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 type 2 diabetes inadequately controlled with metformin or a sulfonylurea monotherapy.<sup>197</sup> The primary outcome variable was the change in HbA1c. Secondary outcomes included the proportion of patients achieving HbA1c of  $< 7$  percent, 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 percent) in HbA1c (both -1.36 percent;  $p < 0.001$  versus baseline). Similar proportions of patients achieved HbA1c  $< 7$  percent (37.5 and 39.8 percent, respectively;  $p = \text{NS}$ ). 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 percent, respectively; the incidence of hypoglycemia was 14.7 and 25.2 percent, respectively ( $p = \text{NS}$ ).

***exenatide extended-release (Bydureon) versus liraglutide (Victoza)***

DURATION 6:<sup>198</sup> In a 26 week, open-label, parallel-group study 912 patients aged 18 years or older with type 2 diabetes 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 percent; 95% CI 0.08-0.33). 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 percent in the liraglutide group versus nine percent in the exenatide group), diarrhea (13 versus six percent, respectively), and vomiting (11 versus four percent, respectively), which occurred less frequently in the exenatide group and with decreasing incidence over time in both groups.

***liraglutide (Victoza) versus glimepiride***

LEAD-3<sup>199</sup>: In this 52-week, controlled trial 746 patients with type 2 diabetes 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 percent with glimepiride versus 0.84 percent with liraglutide 1.2 mg (difference -0.33%; 95% CI, -0.53 to -0.13, p<0.05) and 1.14 percent 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, one patient in 1.8 mg group, and zero patients in the glimepiride group. Discontinuations due to ineffective therapy were 3.6 percent in the liraglutide 1.8 mg group, 6 percent in the liraglutide 1.2 mg group, and 10.1 percent 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<sup>200</sup>: 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 percent with placebo/metformin, decreased by 1 percent with glimepiride/metformin, decreased by 1 percent 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 percent in the liraglutide 1.8 mg/metformin group, 3.3 percent in the liraglutide 1.2 mg/metformin group, 23.8 percent in the placebo/metformin group, and 3.7 percent 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<sup>201</sup>: 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 percent each, p<0.0001), compared with placebo (+0.2 percent, p<0.0001) or rosiglitazone (-0.4 percent, 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 percent), nausea (<11 percent), vomiting (<5 percent) and diarrhea (<8 percent). The percentage of patients who discontinued due to ineffective therapy was three percent in the liraglutide 1.8 mg/glimepiride group, 3.5 percent in the liraglutide 1.2 mg/glimepiride group, 17.5 percent in the placebo/glimepiride group, and 6.9 percent in the rosiglitazone/glimepiride group.

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

LEAD-5<sup>202</sup>: This was 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, all in combination with metformin (1 g twice daily) and glimepiride (4 mg once daily). The liraglutide group resulted in 1.3 percent decrease ( $p<0.0001$ ) in HbA1c compared to 0.2 percent decrease with placebo, and 1.1 percent decrease in the insulin group. The difference in HbA1c for insulin glargine is within the predefined non-inferiority 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 percent nausea, were reported with liraglutide. Discontinuation percentages due to ineffective therapy were 0.9 percent in the liraglutide 1.8 mg group, 0.4 percent in the insulin glargine group, and 11.3 percent 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 percent in each of the liraglutide groups compared to a 0.5 percent decrease in the placebo group.<sup>203</sup> Dose-dependent weight loss occurred with liraglutide 1.2 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 percent in the liraglutide 1.8 mg group, 1.7 percent in the liraglutide 1.2 mg group, and 16.4 percent 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 type 2 diabetes mellitus 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.<sup>204,205</sup> Patients randomized to exenatide started on a dose of 5 mcg twice-daily for four weeks and then were escalated to 10 mcg twice daily. Compared with exenatide, liraglutide 1.8 mg resulted in significant greater reductions in HbA1c (-1.1 percent versus -0.8 percent; 95% CI, -0.47 to -0.18;  $p<0.0001$ ) and more patients achieved an HbA1c value of less than 7 percent (54 versus 43 percent, 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 type 2 diabetes mellitus 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).<sup>206</sup> 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 percent, 95% CI -1.63 to -1.37) and 1.2 mg (-1.24 percent, -1.37 to -1.11) than sitagliptin (-0.9 percent, -1.03 to -0.77). Estimated mean treatment differences for liraglutide versus sitagliptin were -0.6 percent (95% CI -0.77 to -0.43, p<0.0001) for 1.8 mg and -0.34 percent (-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 percent) than with sitagliptin (5 percent). 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).<sup>207</sup> 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 type 2 diabetes mellitus uncontrolled on metformin with or without sulfonylurea.<sup>208</sup> Sulfonylurea was discontinued and injectable liraglutide (1.8 mg/day) was added for 12 weeks as the run-in phase. Subsequently, those with HbA1c  $\geq 7\%$  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 end point was A1C change between randomized groups. Of the patients completing the run-in, 61 percent achieved HbA1c <7% (mean change -1.3% from 7.7% at start), whereas 39 percent did not (-0.6% from 8.3% at start). During run-in, 17 percent withdrew; 46 percent 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 percent of patients with insulin detemir versus 17 percent 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.

## **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.<sup>209</sup> 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 type 2 diabetes 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 cardiovascular 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 meta-analysis including 43 randomized (n=19,101) controlled trials lasting at least 12 weeks involving DPP-4 inhibitors was conducted.<sup>210</sup> 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 percent of participants achieved the HbA1c goal of < 7 percent, which was associated with weight neutrality and no greater hypoglycemia. Baseline HbA1c was the best predictor for achievement of HbA1C target (p<0.001).

## SUMMARY

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

The DPP-4 inhibitors have modest glucose-lowering effects with HbA1c decrements of 0.5 to 1.0%. These agents are weight-neutral and have a low hypoglycemia risk when used as monotherapy or in conjunction with metformin. 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]).

The GLP-1 receptor agonists, **albiglutide (Tanzeum), dulaglutide (Trulicity)**, exenatide (Byetta, Bydureon), liraglutide (Victoza), and the amylin analogue, pramlintide (Symlin) are indicated for patients with type 2 diabetes. Administration of **albiglutide is associated with an HbA1c reduction of 0.7-0.9%, dulaglutide with a reduction of 0.7-1.6%**, and exenatide and liraglutide with a reduction in HbA1c of 0.5-1.6%, based on clinical trials. Many study participants experienced a decrease in weight of 0.4-3.5 kg from baseline. Risks of GLP-1 agonists include the potential for thyroid C-cell tumors including medullary thyroid carcinoma and acute pancreatitis. 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 is dosed once daily, while long-acting **albiglutide, dulaglutide**, and exenatide extended-release (Bydureon) are dosed once weekly.

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