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

March 5, 2017

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, digital scanning, or via any information storage or retrieval system without the express written consent of Magellan Rx Management.

All requests for permission should be mailed to:

Magellan Rx Management
Attention: Legal Department
6950 Columbia Gateway Drive
Columbia, Maryland  21046

The materials contained herein represent the opinions of the collective authors and editors and should not be construed to be the official representation of any professional organization or group, any state Pharmacy and Therapeutics committee, any state Medicaid Agency, or any other clinical committee. This material is not intended to be relied upon as medical advice for specific medical cases and nothing contained herein should be relied upon by any patient, medical professional or layperson seeking information about a specific course of treatment for a specific medical condition. All readers of this material are responsible for independently obtaining medical advice and guidance from their own physician and/or other medical professional in regard to the best course of treatment for their specific medical condition. This publication, inclusive of all forms contained herein, is intended to be educational in nature and is intended to be used for informational purposes only. Send comments and suggestions to PSTCREditor@magellanhealth.com.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>pramlintide (Symlin®)¹</td>
<td>AstraZeneca</td>
<td>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)</td>
</tr>
<tr>
<td>alogliptin (Nesina®)²</td>
<td><em>generic</em>, Takeda</td>
<td>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM)</td>
</tr>
<tr>
<td>alogliptin/metformin (Kazano®)³</td>
<td><em>generic</em>, Takeda</td>
<td>Adjunct to diet and exercise to improve glycemic control in adults with T2DM</td>
</tr>
<tr>
<td>alogliptin/pioglitazone (Oseni®)⁴</td>
<td><em>generic</em>, Takeda</td>
<td>Adjunct to diet and exercise to improve glycemic control in adults with T2DM</td>
</tr>
<tr>
<td>linagliptin (Tradjenta®)⁵</td>
<td>Boehringer Ingelheim</td>
<td>Adjunct to diet and exercise to improve glycemic control in adults with T2DM</td>
</tr>
</tbody>
</table>
| linagliptin/empagliflozin (Glyxambi®)⁶ | Boehringer Ingelheim | Adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both empagliflozin and linagliptin is appropriate  
*Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with T2DM and established cardiovascular disease (CVD); however, effectiveness of linagliptin/empagliflozin on reducing the risk of CV death in adults with T2DM and CVD has not been established* |
| linagliptin/metformin (Jentadueto®)⁷ | Boehringer Ingelheim | Adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both linagliptin and metformin is appropriate                                                                 |
| linagliptin/metformin ER (Jentadueto® XR)⁸ | Boehringer Ingelheim | Adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both linagliptin and metformin ER is appropriate                                                        |
| saxagliptin (Onglyza®)⁹     | AstraZeneca  | Adjunct to diet and exercise to improve glycemic control in adults with T2DM                                                                                                                                       |
| saxagliptin/metformin ER (Kombiglyze® XR)¹⁰ | AstraZeneca | Adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both saxagliptin and metformin is appropriate                                                                 |
| sitagliptin (Januvia®)¹¹    | Merck Sharp & Dohme | Adjunct to diet and exercise to improve glycemic control in adults with T2DM                                                                                                                                       |
| sitagliptin/metformin (Janumet®)¹² | Merck Sharp & Dohme | Adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with sitagliptin and metformin is appropriate                                                                 |
| sitagliptin/metformin extended release (Janumet XR®)¹³ | Merck Sharp & Dohme | Adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both sitagliptin and metformin ER is appropriate                                                                 |
**FDA-Approvals Indications (continued)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>albiglutide (Tanzeum®)14</td>
<td>GlaxoSmithKline</td>
<td>Adjunct to diet and exercise to improve glycemic control in adults with T2DM</td>
</tr>
<tr>
<td>dulaglutide (Trulicity®)15</td>
<td>Eli Lilly</td>
<td>Adjunct to diet and exercise to improve glycemic control in adults with T2DM</td>
</tr>
<tr>
<td>exenatide (Byetta®)16</td>
<td>AstraZeneca</td>
<td>Adjunct to diet and exercise to improve glycemic control in adults with T2DM who are taking metformin, a sulfonylurea, thiazolidinedione (TZD), or a combination of metformin and a sulfonylurea or TZD but have not achieved adequate glycemic control Add-on therapy to insulin glargine, with or without metformin and/or a TZD, in conjunction with diet and exercise for adults with T2DM who are not achieving adequate glycemic control on insulin glargine alone</td>
</tr>
<tr>
<td>exenatide ER (Bydureon®)17</td>
<td>AstraZeneca</td>
<td>Adjunct to diet and exercise to improve glycemic control in adults with T2DM</td>
</tr>
<tr>
<td>liraglutide (Victoza®)18</td>
<td>Novo Nordisk</td>
<td>Adjunct to diet and exercise to improve glycemic control in adults with T2DM</td>
</tr>
<tr>
<td>liraglutide/insulin degludec (Xultophy®)19</td>
<td>Novo Nordisk</td>
<td>Adjunct to diet and exercise to improve glycemic control in adults with T2DM inadequately controlled on basal insulin (&lt; 50 units daily) or liraglutide (≤ 1.8 mg daily)</td>
</tr>
<tr>
<td>lixisenatide (Adlyxin®)20</td>
<td>Sanofi</td>
<td>Adjunct to diet and exercise to improve glycemic control in adults with T2DM</td>
</tr>
<tr>
<td>lixisenatide/insulin glargine (Soliqua™)21</td>
<td>Sanofi</td>
<td>Adjunct to diet and exercise to improve glycemic control in adults with type T2DM inadequately controlled on basal insulin (&lt; 60 units daily) or lixisenatide</td>
</tr>
</tbody>
</table>

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

Albiglutide (Tanzeum), exenatide (Byetta, Bydureon), liraglutide (Victoza), liraglutide/insulin degludec (Xultophy), lixisenatide (Adlyxin), and lixisenatide/insulin glargine (Soliqua) have not been studied in combination with prandial insulin. Exenatide ER (Bydureon) has not been studied in combination with basal insulin.

Albiglutide (Tanzeum), dulaglutide (Trulicity), exenatide (Byetta, Bydureon), liraglutide (Victoza), liraglutide/insulin degludec (Xultophy), lixisenatide (Adlyxin), linagliptin (Tradjenta), linagliptin/empagliflozin (Glyxambi), linagliptin/metformin (Jentadueto), linagliptin/metformin ER (Jentadueto XR), lixisenatide/insulin glargine (Soliqua), saxagliptin (Onglyza), saxagliptin/metformin ER (Kombiglyze XR), sitagliptin (Januvia), sitagliptin/metformin (Janumet), and sitagliptin/metformin ER (Janumet XR) have not been studied in patients with a history of pancreatitis. Labeling for alogliptin-containing agents (Kazano, Nesina, Oseni) advise that it is unknown if these agents lead to an increased risk of pancreatitis in patients with a history of the condition.

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

Initial treatment for type 2 diabetes (T2DM) consists of diet, exercise, and metformin, followed by other oral antidiabetic agents and/or exogenous insulin. While this approach improves glycemic control, beta-cell function cannot be completely restored. Available therapies do not correct defects in secretion of other hormones in the glycemic control pathway. In addition to insulin resistance and decreased insulin production, T2DM is characterized by insufficient secretion of the neuroendocrine hormone, amylin, from the pancreatic beta-cells and incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotrophic polypeptide (GIP), from the gastrointestinal tract. 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) Standards of Medical Care in Diabetes, 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. It is generally agreed that metformin, if not contraindicated and if tolerated, is the preferred first agent in the treatment of T2DM. If metformin cannot be used, another oral agent could be chosen, such as a sulfonylurea (SU), thiazolidinedione (TZD), 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 doses does not achieve or maintain the hemoglobin A1c (HbA1c) target over 3 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 1%. The ADA advises that a reasonable HbA1c goal for nonpregnant adults is < 7%; however, more stringent HbA1c goals of < 6.5% for select patients (e.g., those with short duration of diabetes, long life expectancy, and no significant cardiovascular (CV) disease [CVD]) may be considered if this can be achieved without significant hypoglycemia. Less-stringent HbA1c goals (< 8%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain. For pediatric patients, the ADA now recommends a target HbA1c of < 7.5% for all age-groups, although individualization is still supported. During pregnancy, there is an increase in red blood cell turnover which is reflected by a decrease in HbA1c levels. In addition, HbA1c represents an average and should be used as a secondary measure, next to self-monitoring of blood glucose. The ADA recommends a target HbA1c during pregnancy of 6% to 6.5%; 6% is optimal if this can be achieved without significant hypoglycemia. Due to the altered red blood cell kinetics during pregnancy, more frequent (e.g., monthly) monitoring of HbA1c levels may be required.

In 2017, the American Academy of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) updated their algorithm and practice guidelines for the management of T2DM. A treatment goal of HbA1c ≤ 6.5% for healthy patients with low hypoglycemic risk is recommended; for patients with concurrent illness and at risk of hypoglycemia, a goal HbA1c > 6.5% is appropriate. Lifestyle modification, including medically-assisted weight loss, underlies all treatments, as obesity is a risk factor for T2DM and microvascular complications. Choice of antidiabetic therapy should be based on cost, ease of use, other medication and patient risk factors, and the patient’s initial HbA1c level. Patients with an HbA1c ≥ 7.5% should begin with dual therapy with metformin plus another agent.
Patients with an HbA1c > 9% and no symptoms may start 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 3 months and failure to improve may warrant additional complementary therapy for optimal glycemic control. The guidelines provide prescribers a hierarchical order of the usage of drugs where metformin is the preferred treatment of choice for monotherapy and first-line agent for dual- and triple-therapy. For patients with HbA1c < 7.5% at entry, monotherapy options that are considered safe are metformin, a GLP-1 receptor agonist, sodium-dependent glucose cotransporter 2 (SGLT2) inhibitor, DPP-4 inhibitor, or alpha-glucosidase inhibitor. AACE/ACE indicate that liraglutide and empagliflozin (a component of Glyxambi) may offer renal and CV benefit. They also suggest that saxagliptin and alogliptin may be associated with possible CV risk; there may be increased risk of bone fractures with canagliflozin; and increased congestive heart failure (HF) risk with sulfonylureas, glinides, and insulin. Medications to be used with caution include TZDs and sulfonylureas.

In 2017, the American College of Physicians (ACP) updated their recommendations for oral pharmacologic therapy for T2DM. They recommend metformin as first-line therapy and advise that it can be safely used in patients with mild renal impairment and in select patients with moderate impairment. They recommend to add a SU, TZD, SGLT-2 inhibitor, or DPP-4 inhibitor as second-line therapy.

**PHARMACOLOGY**

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

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

The GLP-1 agonist agents, albiglutide (Tanzeum), dulaglutide (Trulicity), exenatide (Byetta, Bydureon), liraglutide (Victoza), and lixisenatide (Adlyxin) 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 dosed twice daily. The exenatide ER formulation (Bydureon) releases exenatide from microspheres over a period of about 10 weeks and allows for once weekly dosing. Albiglutide (Tanzeum) and dulaglutide (Trulicity) have a longer half-life due, at least in part, to a decreased DPP-4 degradation in the body, making them appropriate for once weekly dosing. 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.
Liraglutide/insulin degludec (Xultophy) and lixisenatide/insulin glargine (Soliqua) combine a GLP-1 receptor agonist with a long-acting insulin analogue. Insulin lowers blood glucose levels by stimulating peripheral glucose uptake by skeletal muscle and fat, and by inhibiting gluconeogenesis. Insulin also inhibits lipolysis in the adipocyte, inhibits proteolysis, and enhances protein synthesis.

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

Alogliptin/metformin (Kazano), linagliptin/metformin (Jentadueto), saxagliptin/metformin ER (Kombiglyze XR), sitagliptin/metformin (Janumet), and sitagliptin/metformin ER (Janumet XR) combine a DPP-4 enzyme inhibitor with metformin. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Alogliptin/pioglitazone (Oseni) combines a DPP-4 enzyme inhibitor with a TZD. Pioglitazone is a peroxisome proliferator-activated receptor-gamma agonist that improves insulin sensitivity in muscle and adipose tissue and inhibits hepatic gluconeogenesis. Linagliptin/empagliflozin (Glyxambi) combines a DPP-4 enzyme inhibitor with a sodium-glucose cotransporter-2 (SGLT2) inhibitor that increases urinary glucose excretion by inhibiting SGLT2, the major transporter responsible for the reabsorption of filtered glucose from the kidney.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Peak (hrs)</th>
<th>Half-life (hrs)</th>
<th>Metabolism</th>
<th>Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amylin Analogue</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pramlintide (Symlin)</td>
<td>0.33</td>
<td>0.8</td>
<td>Primarily by kidneys to deslys pramlintide (active metabolite)</td>
<td>--</td>
</tr>
<tr>
<td><strong>DPP-4 Enzyme Inhibitors Containing Products</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>saxagliptin (Onglyza)</td>
<td>2 (parent drug)</td>
<td>2.5 (parent drug)</td>
<td>CYP3A4/5; active metabolite – 5-hydroxy saxagliptin which is one-half as potent as saxagliptin</td>
<td>Urine: 75%; Feces: 22%</td>
</tr>
<tr>
<td></td>
<td>4 (active metabolite)</td>
<td>3.1 (active metabolite)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sitagliptin (Januvia)</td>
<td>1-4</td>
<td>12.4</td>
<td>Primarily by CYP3A4 (minor)</td>
<td>Urine: 87%; Feces 13%</td>
</tr>
<tr>
<td>linagliptin (Tradjenta)</td>
<td>1.5</td>
<td>12</td>
<td>90% unchanged, no active metabolite</td>
<td>Urine: 5%; Feces: 80%</td>
</tr>
<tr>
<td>empagliflozin</td>
<td>1.5</td>
<td>12.4</td>
<td>hepatic (O-glucuronidation via UGT1A3 &amp; 1A8, &amp; 1A9)</td>
<td>Urine: 54.4%; Feces: 41.2%</td>
</tr>
<tr>
<td>metformin</td>
<td>4-8</td>
<td>6.2</td>
<td>None</td>
<td>Excreted unchanged in the urine</td>
</tr>
<tr>
<td>pioglitazone</td>
<td>2</td>
<td>3-7 (parent drug)</td>
<td>16-24 (metabolites)</td>
<td>Urine: 15%-30%; Feces: majority</td>
</tr>
</tbody>
</table>

**GLP-1 Receptor Agonists**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Peak (hrs)</th>
<th>Half-life (hrs)</th>
<th>Metabolism</th>
<th>Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>albiglutide (Tanzeum)</td>
<td>3-5 days</td>
<td>5 days</td>
<td>Protein catabolism</td>
<td>nr</td>
</tr>
<tr>
<td>alogliptin (Nesina)</td>
<td>1-2</td>
<td>21</td>
<td>Active metabolite: N-demethylated alogliptin &lt; 1% of the parent compound</td>
<td>Urine: 76%; Feces: 13%</td>
</tr>
<tr>
<td>dulaglutide (Trulicity)</td>
<td>24-72</td>
<td>5 days</td>
<td>Protein catabolism</td>
<td>nr</td>
</tr>
<tr>
<td>exenatide (Byetta)</td>
<td>2.1</td>
<td>2.4</td>
<td>Predominantly by the kidneys</td>
<td>Predominantly by the kidneys</td>
</tr>
<tr>
<td>exenatide ER (Bydureon)</td>
<td>Peak 1: 2 weeks</td>
<td>Peak 2: 6-7 Weeks</td>
<td>Predominantly by the kidneys</td>
<td>Predominantly by the kidneys</td>
</tr>
<tr>
<td>liraglutide (Victoza)</td>
<td>8-12</td>
<td>13</td>
<td>Metabolized in a similar manner to large proteins without a specific organ as a major route of elimination.</td>
<td>Minimally excreted in urine (6%) and feces (5%) as metabolites</td>
</tr>
</tbody>
</table>
Pharmacokinetics (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Peak (hrs)</th>
<th>Half-life (hrs)</th>
<th>Metabolism</th>
<th>Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1 Receptor Agonists (continued)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lixisenatide (Adlyxin)</td>
<td>1-3.5</td>
<td>3</td>
<td>Glomerular filtration and proteolytic degradation</td>
<td>Predominantly by the kidneys</td>
</tr>
<tr>
<td>insulin degludec (component of Xultophy)</td>
<td>9</td>
<td>25</td>
<td>In active metabolites</td>
<td>nr</td>
</tr>
<tr>
<td>insulin glargine (component of Soliqua)</td>
<td>5 (no actual peak as insulin glargine is released slowly over 24 hours)</td>
<td>nr</td>
<td>Partly metabolized at the carboxyl terminus of the B chain</td>
<td>nr</td>
</tr>
</tbody>
</table>

In bioequivalence studies, alogliptin/metformin (Kazano), alogliptin/pioglitazone (Oseni), linagliptin/empagliflozin (Glyxambi), linagliptin/metformin (Jentadueto), linagliptin/metformin ER (Jentadueto XR), saxagliptin/metformin ER (Kombiglyze XR), sitagliptin/metformin (Janumet), and sitagliptin/metformin ER (Janumet XR) were found to be bioequivalent to the single agents administered together. The combination of lixisenatide and insulin glargine does not impact the pharmacodynamics of insulin glargine; it is not known if the combination has an impact on lixisenatide pharmacodynamics. Overall, the pharmacokinetics of insulin degludec and liraglutide were not affected in a clinically relevant manner when administered as a combination product.

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

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

CONTRAINDICATIONS/WARNINGS

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, except empagliflozin (Jardiance), liraglutide (Victoza), and lixisenatide (Adlyxin). Empagliflozin is a component of Glyxambi; however, effectiveness of linagliptin/empagliflozin on reducing the risk of CV death in adults with T2DM and CVD has not been established. Data from 3 CVD outcome RCTs with alogliptin, saxagliptin, and sitagliptin report no harm but did not show any benefit on major CVD events. A modest but significant increased risk of hospitalization for heart failure (HF) was observed with saxagliptin and with alogliptin (only in subjects with no history of HF), but not with sitagliptin.
In March 2013, the FDA published an alert stating that patients with T2DM treated with DPP-4 inhibitors or GLP-1 agonists may be at increased risk of pancreatitis and pre-cancerous cellular changes (pancreatic duct metaplasia). This warning is based on examination of a small number of pancreatic tissue specimens taken from patients after death due to unspecified causes. Subsequently, in March 2014, based on review of toxicology studies that showed no incretin-associated adverse effects on the pancreas, the FDA and European Medicines Agency (EMA) announced that they have not reached a final conclusion about a causal relationship between the use of incretin-based drugs and pancreatitis or pancreatic cancer. Both agencies continue to investigate this safety signal.

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

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

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

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

**Amylin Analogue**

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

Pramlintide should only be considered in patients who have failed to achieve adequate glycemic control on insulin. Patients who are not candidates for pramlintide include patients with HbA1c > 9% or who require use of drugs that stimulate gastrointestinal (GI) motility.
DPP-4 Enzyme Inhibitors

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

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

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

The EXAMINE study showed that the primary endpoint (CV death, nonfatal MI, and nonfatal stroke) occurred at similar rates for alogliptin and placebo in 5,380 patients with diabetes and an acute MI/unstable angina requiring hospitalization.85

The SAVOR TIMI-53 study evaluated CV outcomes with saxagliptin in patients (n = 16,492) with T2DM, an estimated glomerular filtration rate [eGFR] ≤ 50 mL/minute) and a history of or at risk for CV events.86 Saxagliptin had no effect on the composite of CV death, myocardial infarction (MI), or ischemic stroke, but was associated with an increased rate of hospitalization for heart failure (HF). The results of the SAVOR-TIMI 53 CV outcomes trial prompted the FDA to investigate the possible association between DPP-4 inhibitors and HF.87 The FDA’s review concluded that medicines containing saxagliptin or alogliptin may increase the risk of HF, particularly in patients with pre-existing cardiac or renal disease.88 Both agents were associated with increased rates of hospitalization for HF compared to placebo (saxagliptin 3.5% versus 2.8%, respectively; alogliptin 3.9% versus 3.3%, respectively).

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

A national commercially-insured U.S. database was used to evaluate the association of sitagliptin and HF.89 In the analysis, 7,620 patients were identified with incident HF and also having T2DM. Subjects subsequently using sitagliptin were compared with those not using sitagliptin in the 90 days before the occurrence of all-cause hospital admission or death. The analysis found that there was no increased...
risk of all-cause hospitalization or death associated with sitagliptin use; however, there was an increased risk of HF-related hospitalization among this cohort. In addition, the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) evaluated the impact of sitagliptin on CV risk in 14,671 patients with T2DM and CV disease. After a median of 3 years, sitagliptin did not result in an increased risk of CV events, including hospitalization for HF, as measured by the primary outcome of a composite of CV death, nonfatal myocardial infarction (MI), nonfatal stroke, or hospitalization for unstable angina.

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

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

Linagliptin/empagliflozin (Glyxambi) is contraindicated in patients with severe renal impairment, end-stage renal disease (ESRD), or dialysis due to the SGLT2 inhibitor component. Renal function should be evaluated prior to initiating therapy and periodically thereafter.

The FDA identified a potential increased risk of ketoacidosis and urosepsis in patients taking SGLT2 inhibitors, including empagliflozin (Glyxambi). Patients should seek immediate medical attention if they experience difficulty breathing, nausea, vomiting, abdominal pain, confusion, and unusual fatigue or sleepiness. Empagliflozin should be discontinued if acidosis is confirmed.

Symptomatic hypotension can occur after starting empagliflozin due to osmotic diuresis leading to intravascular volume contraction. This is particularly seen in patients with impaired renal function (estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m²), elderly patients, patients with low systolic blood pressure, and patients on diuretics or drugs which interfere with the renin-angiotensin-aldosterone system. Volume status should be assessed and corrected prior to starting empagliflozin therapy and monitored thereafter.

Empagliflozin increases the risk for urinary tract infections and genital mycotic infections and may increase low-density lipoprotein cholesterol (LDL-C) levels. Monitor and treat patients appropriately.

In 2016, an updated FDA review confirmed preclinical and clinical trial data and results from an observational study suggest an increased risk of bladder cancer in pioglitazone users. The observational data further suggest that the risk increases with duration of use. Do not use alogliptin/pioglitazone (Oseni) in patients with active bladder cancer. Use caution when using in patients with a prior history of bladder cancer.
Fatal and non-fatal hepatic failure have been reported in patients taking alogliptin and pioglitazone. It is recommended that a liver function test be performed prior to beginning alogliptin (Nesina, Oseni) therapy, particularly if prescribed with pioglitazone; therapy may be started with caution, if abnormal test results are produced.

Combination products containing metformin (Janumet, Janumet XR, Jentadueto, Jentadueto XR, Kazano, Kombiglyze XR) carry a boxed warning for lactic acidosis due to the accumulation of the metformin component. The risk increases with conditions such as age ≥ 65 years, radiological studies (with contrast, surgery, hypoxic state), excess alcohol intake, and hepatic insufficiency. Symptoms include malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include blood lactate, anion gap acidosis, lactate/pyruvate ratio, and metformin plasma level > 5 mcg/mL. If acidosis is suspected, DPP-4 inhibitor/metformin therapy should be discontinued and the patient hospitalized immediately; prompt hemodialysis is recommended as metformin is substantially secreted by the kidney. Metformin is contraindicated in patients with an eGFR < 30 mL/min/1.73m². In addition, impaired hepatic function has been associated with some cases of lactic acidosis; metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients treated with metformin-containing regimens should be advised to avoid excessive alcohol intake.

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.

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

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

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

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

**GLP-1 Receptor Agonists**

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

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

Acute pancreatitis has been reported in association with albiglutide and dulaglutide in clinical trials. Post-marketing reports of pancreatitis, including fatal and non-fatal hemorrhagic necrotizing pancreatitis, have occurred with exenatide (Bydureon, Byetta), liraglutide, and lixisenatide use. After therapy initiation with any of the agents, patients should be observed for symptoms of pancreatitis and the drug discontinued if pancreatitis is suspected. The drug should not be restarted if pancreatitis is confirmed.

Use of GLP-1 agonists has been associated with gastrointestinal adverse reactions. Use of these agents has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis; therefore, they are not recommended for patients with severe gastrointestinal disease. Exenatide (Byetta), liraglutide, and lixisenatide dosages are titrated during the first 1 to 4 weeks (depending on the product) 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 reports have been in patients without known underlying renal disease. Some of the events occurred in patients receiving 1 or more medications known to affect renal function or hydration status. Nausea, vomiting, diarrhea, or dehydration was reported by the majority of patients who experienced acute renal failure or worsening of chronic renal failure. Since these gastrointestinal reactions may worsen renal function, caution should be used with initiating or increasing doses of these agents in patients with renal impairment. Reversibility of altered renal function has been observed with supportive treatment and discontinuation of potentially causative agents.

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

Glucose lowering with GLP-1 agonists is not associated with an inherently high risk of hypoglycemia. However, when GLP-1 agonists are used in combination with an insulin secretagogue or insulin, patients may be at increased risk for hypoglycemic episodes. Reduced dosage of the insulin secretagogue or insulin may be required. However, the combination products, liraglutide/insulin degludec and lixisenatide/insulin glargine, are contraindicated during episodes of hypoglycemia, due to their insulin component.

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 5% and 10% of subjects on albiglutide and liraglutide, respectively, formed antibodies to the drug; however, efficacy and safety were not affected. In clinical studies, 70% of lixisenatide-treated patients developed antibodies to lixisenatide at week 24 of therapy. An increased incidence of allergic and injection site reactions may occur in antibody positive patients. A subset of patients with the highest antibody concentration to lixisenatide...
(2.4%) reported reduced glycemic response. No dulaglutide anti-drug antibodies were found in clinical pharmacology studies. The potential exists for the development of antibodies to insulin.

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

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

Risk Evaluation and Mitigation Strategies (REMS)

Albiglutide (Tanzeum), dulaglutide (Trulicity), exenatide ER (Bydureon), liraglutide (Victoza), and liraglutide/insulin degludec (Xultophy) are subject to a communication plan to inform healthcare providers and patients of the risk of acute pancreatitis and medullary thyroid carcinoma. Pramlintide (Symlin) was subject to a communication plan; however, its REMS program was removed in 2017.

Medication Guides are maintained for all incretin mimetic agents regardless of REMS requirements.

DRUG INTERACTIONS

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

Some medications can predispose patients to hyperglycemia and may lead to loss of glycemic control. These medications include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid. Patients should be closely observed for changes in glycemic control when starting or stopping these medications.

Amylin Analogue

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

DPP-4 Enzyme Inhibitors

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

Concomitant use of linagliptin (Tradjenta, Glyxambi, Jentadueto, Jentadueto XR) 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.
Saxagliptin (Onglyza) is metabolized primarily by the cytochrome P450 3A4/5 (CYP3A4/5) enzymes. Drugs that are strong inhibitors of these enzymes can significantly increase the exposure of saxagliptin. The dose for saxagliptin should be limited to 2.5 mg when co-administered with strong CYP3A4/5 inhibitors, such as ketoconazole, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin. Dosage adjustment of saxagliptin is not recommended when given concomitantly with drugs that are inducers or moderate inhibitors of 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.

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

Concurrent use of metformin-containing products (Janumet, Janumet XR, Jentadueto, Jentadueto XR, Kazano, 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, 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 healthy volunteers with a 60% 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 metformin-containing DPP4-inhibitors should be considered in patients who are taking cationic medications.

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

**GLP-1 Receptor Agonists**

GLP-1 inhibitors may also affect gastric emptying time and may reduce the extent and rate of absorption of orally-administered drugs that are given concomitantly. Patients should take oral medications at least 1 hour before exenatide, lixisenatide, and lixisenatide/insulin glargine injections. In clinical trials, 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. Oral contraceptives should be taken at least 1 hour before lixisenatide/insulin glargine administration or 11 hours after the dose.

When used in combination with metformin, no increase in the incidence of hypoglycemia was observed with GLP-1 agonists compared to placebo. However, GLP-1 agonist use with an insulin secretagogue, such as a sulfonylurea, or insulin may increase the incidence of hypoglycemia. A reduced dose of the insulin secretagogue or insulin may be needed.
There are post-marketing reports of increased international normalized ratio (INR), sometimes associated with bleeding, with concomitant use of warfarin and exenatide (Byetta); however, exenatide was not shown to have a significant effect on INR in a clinical study. Exenatide ER (Bydureon) 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 of lovastatin by 40% and delayed the time to maximum serum concentration (Tmax) and decreased maximum serum concentration (Cmax) of lovastatin. However, in a 30-week clinical trial, concurrent use of the medications was not associated with consistent changes in lipid profiles.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Nausea</th>
<th>Vomiting</th>
<th>Diarrhea</th>
<th>Headache</th>
<th>Hypoglycemia</th>
<th>URI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amylin Analogue</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pramlintide (Symlin)</td>
<td>28-48</td>
<td>8-11</td>
<td>nr</td>
<td>5-13</td>
<td>4.7-16.8</td>
<td>nr</td>
</tr>
<tr>
<td></td>
<td>(12-17)</td>
<td>(4-7)</td>
<td></td>
<td>(7)</td>
<td>(2.1-10.8)</td>
<td></td>
</tr>
<tr>
<td><strong>DPP-4 Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>alogliptin (Nesina)</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>4.2</td>
<td>1.5</td>
<td>4.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(2.5)</td>
<td>(1.6)</td>
<td>(2.1)</td>
</tr>
<tr>
<td>alogliptin/metformin (Kazano)</td>
<td>25.5</td>
<td>25.5</td>
<td>5.5</td>
<td>5.3</td>
<td>1.9</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td>(8.3)</td>
<td>(8.3)</td>
<td>(2.8)</td>
<td>(2.8)</td>
<td>(1.8)</td>
<td>(2.8)</td>
</tr>
<tr>
<td></td>
<td>(metformin monotherapy)</td>
<td>(metformin monotherapy)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>alogliptin/ pioglitazone (Oseni)</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>reported</td>
<td>0.8-3.8</td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.8)</td>
<td>(3.3)</td>
</tr>
<tr>
<td>linagliptin (Tradjenta)</td>
<td>nr</td>
<td>nr</td>
<td>3.3</td>
<td>reported</td>
<td>7.6</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(3)</td>
<td></td>
<td>(4.1)</td>
<td>(1.1)</td>
</tr>
<tr>
<td>linagliptin/empagliflozin (Glyxambi)</td>
<td>1.1-2.3</td>
<td>3-3.3</td>
<td>nr</td>
<td>nr</td>
<td>2.2-3.6</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>(empagliflozin monotherapy)</td>
<td>(linagliptin monotherapy)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>linagliptin/metformin (Jentadueto, Jentadueto XR)</td>
<td>reported</td>
<td>reported</td>
<td>6.3</td>
<td>nr</td>
<td>reported</td>
<td>nr</td>
</tr>
<tr>
<td>saxagliptin (Onglyza)</td>
<td>nr</td>
<td>2.2-2.3</td>
<td>nr</td>
<td>6.5</td>
<td>4.0-5.6</td>
<td>7.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1.3)</td>
<td></td>
<td>(5.9)</td>
<td>(4.1)</td>
<td>(7.6)</td>
</tr>
<tr>
<td>saxagliptin/ metformin ER (Kombiglyze XR)</td>
<td>nr</td>
<td>nr</td>
<td>6.9</td>
<td>7.5</td>
<td>3.4-7.8</td>
<td>nr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(11.2)</td>
<td>(5.2)</td>
<td>(5)</td>
<td></td>
</tr>
<tr>
<td>sitagliptin (Januvia)</td>
<td>1.4</td>
<td>nr</td>
<td>3</td>
<td>1.1-5.9</td>
<td>0.6-15.5</td>
<td>4.5-6.3</td>
</tr>
<tr>
<td></td>
<td>(0.6)</td>
<td></td>
<td>(2.3)</td>
<td>(2.8-4.6)</td>
<td>(0.6-1.8)</td>
<td>(3.4-5.1)</td>
</tr>
<tr>
<td>sitagliptin/metformin (Janumet, Janumet XR)</td>
<td>4.8</td>
<td>2.2</td>
<td>7.5</td>
<td>5.9</td>
<td>15.3-16.4</td>
<td>6.2</td>
</tr>
<tr>
<td></td>
<td>(1.1)</td>
<td>(0.6)</td>
<td>(4.0)</td>
<td>(2.8)</td>
<td>(0.9-8.2)</td>
<td>(5.1)</td>
</tr>
</tbody>
</table>
### Adverse Effects (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Nausea</th>
<th>Vomiting</th>
<th>Diarrhea</th>
<th>Headache</th>
<th>Hypoglycemia</th>
<th>URI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GLP-1 Receptor Agonists</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>albiglutide (Tanzeum)</td>
<td>11.1</td>
<td>4.2</td>
<td>13.1</td>
<td>nr</td>
<td>2</td>
<td>14.2</td>
</tr>
<tr>
<td></td>
<td>(9.6)</td>
<td>(2.6)</td>
<td>(10.5)</td>
<td></td>
<td>(2)</td>
<td>(13)</td>
</tr>
<tr>
<td>dulaglutide (Trulicity)</td>
<td>12.4-21.1</td>
<td>6-12.7</td>
<td>8.9-12.6</td>
<td>nr</td>
<td>2.6-5.6</td>
<td>nr</td>
</tr>
<tr>
<td></td>
<td>(5.3)</td>
<td>(2.3)</td>
<td>(6.7)</td>
<td></td>
<td>(0)</td>
<td></td>
</tr>
<tr>
<td>exenatide (Byetta)</td>
<td>8-44</td>
<td>4-13</td>
<td>≥1-13</td>
<td>9</td>
<td>3.8-35.7</td>
<td>nr</td>
</tr>
<tr>
<td></td>
<td>(0-18)</td>
<td>(0-4)</td>
<td>(0-6)</td>
<td>(6)</td>
<td>(3.3-12.6)</td>
<td></td>
</tr>
<tr>
<td>exenatide ER (Bydureon)</td>
<td>11.3-27</td>
<td>10.8-11.3</td>
<td>9.3-20</td>
<td>6.1-9.9</td>
<td>0-20</td>
<td>nr</td>
</tr>
<tr>
<td>liraglutide (Victoza)</td>
<td>18-20</td>
<td>6-9</td>
<td>10-12</td>
<td>10-11</td>
<td>3.6-27.4</td>
<td>6-7</td>
</tr>
<tr>
<td></td>
<td>(5)</td>
<td>(2)</td>
<td>(4)</td>
<td>(7)</td>
<td>(2.5-16.7)</td>
<td>(6)</td>
</tr>
<tr>
<td>liraglutide/insulin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>degludec (Xultophy)</td>
<td>7.8</td>
<td>reported</td>
<td>7.5</td>
<td>9.1</td>
<td>reported</td>
<td>5.7</td>
</tr>
<tr>
<td>lixisenatide (Adlyxin)</td>
<td>25</td>
<td>10</td>
<td>8</td>
<td>9</td>
<td>2</td>
<td>nr</td>
</tr>
<tr>
<td></td>
<td>(6)</td>
<td>(2)</td>
<td>(6)</td>
<td>(6)</td>
<td>(2)</td>
<td></td>
</tr>
<tr>
<td>lixisenatide/insulin glargine (Soliqua)</td>
<td>10</td>
<td>nr</td>
<td>7</td>
<td>5.4</td>
<td>25.6-40</td>
<td>5.5</td>
</tr>
</tbody>
</table>

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.

Risk of hypoglycemia increases in patients treated when a DPP-4 inhibitor or GLP-1 agonist is used in combination with a 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 ER (Bydureon) included gastroesophageal reflux (7.4%), constipation (6.3% to 10.1%), dyspepsia (5% to 7.3%), decreased appetite (5%), and fatigue (5.6% to 6.1%). Dyspepsia and gastroesophageal reflux was also reported with exenatide (Byetta) use (6% and 3%, respectively).

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

Other common adverse reactions reported more often with dulaglutide (Trulicity) compared to placebo are abdominal pain (6.5% to 9.4%) and decreased appetite (4.9% to 8.6%).
In 5 comparator-controlled 24 to 30 week trials, injection site reactions were observed more frequently in patients treated with exenatide ER (Bydureon; 17.1%) than in patients treated with exenatide (Byetta; 12.7%). One percent of patients treated with exenatide ER (Bydureon) withdrew due to injection site adverse reactions (injection site mass, injection site nodule, injection site pruritus, and injection site reaction). Cases of serious injection-site reactions, including abscess, cellulitis, and necrosis, have been reported post-marketing with exenatide ER (Bydureon) use.

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

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

### Special Populations

#### Pediatrics

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

#### Pregnancy

Linagliptin (Tradjenta), linagliptin/metformin (Jentadueto), sitagliptin (Januvia), sitagliptin/metformin (Janumet), and sitagliptin/metformin ER (Janumet XR) are Pregnancy Category B. Pramlintide (Symlin), albiglutide (Tanzeum), exenatide (Byetta, Bydureon), and liraglutide (Victoza) are Pregnancy Category C. Linagliptin/empagliflozin (Glyxambi) is not recommended during the second and third trimesters of pregnancy, due to data in animals showing adverse renal effects of empagliflozin.

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

### Renal Insufficiency

Metformin-containing products (Kazano, Kombiglyze XR, Janumet, Janumet XR, Jentadueto, Jentadueto XR) in this review are contraindicated in patients with an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m². Alogliptin/metformin (Kazano), is not recommended in those with eGFR 30 to 60 mL/min/1.73m²; the remainder of the metformin-containing products are not recommended with eGFR 30 to 45 mL/min/1.73m² and, if eGFR falls below 45 mL/min/1.73m² during therapy with these products, benefits and risks of continued therapy should be assessed.

Use pramlintide, albiglutide, dulaglutide, liraglutide, and lixisenatide with caution in patients with renal impairment; no dosage adjustment is needed.
Exenatide is not recommended for use in patients with a creatinine clearance (CrCl) < 30 mL/min or ESRD. **Liraglutide/insulin degludec (Xultophy)** has not been studied in patients with severe renal impairment. Lixisenatide (Adlyxin) has not been studied in patients with ESRD and is, therefore, not recommended in this population. Patients with renal impairment may require more frequent glucose monitoring as this population may have increase circulating levels of insulin. There is limited therapeutic experience in patients with end stage renal disease (eGFR < 15 mL/min/1.73 m²) and insulin glargine/lixisenatide is not recommended for use in this population.

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

Linagliptin/empagliflozin (Glyxambi) is contraindicated in patients with severe renal impairment, ESRD, or who are on dialysis.

No dose adjustments for saxagliptin (Onglyza) are necessary for patients with mild renal impairment, but patients with eGFR < 45 mL/min/1.73m² should receive saxagliptin 2.5 mg once daily. Saxagliptin is removed by hemodialysis.

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 ESRD on dialysis, the recommended daily dose of sitagliptin is 25 mg.

**Hepatic Insufficiency**

Pramlintide has not been studied in patients with hepatic impairment.

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

No dosage adjustment of albiglutide (Tanzeum), exenatide (Byetta), exenatide ER (Bydureon), liraglutide (Victoza), **lixisenatide (Adlyxin)**, linagliptin (Tradjenta), linagliptin/empagliflozin (Glyxambi), 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, **linagliptin/metformin ER**, saxagliptin/metformin ER, sitagliptin/metformin, and sitagliptin/metformin ER use should be avoided in patients with hepatic disease.

**Elderly**

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

Due to the SGLT2 inhibitor component, linagliptin/empagliflozin (Glyxambi) could affect the hydration status in patients 75 years of age and older and could have decreased efficacy in those with renal impairment in this age group.
No overall differences in safety or efficacy of the remaining products in this class were observed between patients 65 years and older and younger patients. However, since elderly patients are more likely to have decreased renal function, use of these agents in this population should be considered carefully, particularly with agents that also contain metformin which is substantially excreted by the kidney.

### DOSAGES

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Time of Administration Related to Mealtime</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amylin Analogue</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| pramlintide (Symlin) | T1DM: initiate at 15 mcg SC injection, titrate to 30 or 60 mcg by 15 mcg increments  
T2DM: initiate at 60 mcg SC injection, titrate to 120 mcg as tolerated | Prior to major meals, concurrently with insulin; decrease insulin doses 50% initially, then adjust only after reaching the target dose of pramlintide | 1.5 mL, 2.7 mL pens (1 mg/mL) |
| **DPP-4 Enzyme Inhibitors** | | | |
| alogliptin (Nesina) | 25 mg once daily | Administer without regard to food | 6.25 mg, 12.5 mg, 25 mg tablets |
| alogliptin/metformin (Kazano) | 1ne tablet twice daily; adjust dose based on effectiveness and tolerability; Do not exceed 25 mg/2000 mg per day | Administer with food | 12.5/500 mg, 12.5/1,000 mg tablets |
| alogliptin/pioglitazone (Oseni) | 1 tablet once daily; do not exceed 25 mg/45 mg per day | Administer without regard to food | 12.5/15 mg, 12.5/30 mg, 12.5/45 mg, 25/15 mg, 25/30 mg, 25/45 mg tablets |
| linagliptin (Tradjenta) | 5 mg once daily | Take with or without food | 5 mg tablet |
| linagliptin/empagliflozin (Glyxambi) | 5 mg/10 mg once daily in the morning; may increase to 5 mg/25 mg once daily | Take with or without food | 5/10 mg, 5/25 mg tablets |
| 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 | 2.5/500 mg, 2.5/850 mg, 2.5/1,000 mg tablets |
### Dosages (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Time of Administration Related to Mealtime</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DPP-4 Enzyme Inhibitors (continued)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| linagliptin/metformin ER (Jentadueto XR) | Starting dose:  
In patients not already taking metformin: 5 mg linagliptin/1,000 mg metformin ER once daily  
In patients already taking metformin: 5 mg linagliptin and a similar total daily dose of metformin once daily  
In patients already taking linagliptin and metformin or Jentadueto: switch to Jentadueto XR containing 5 mg linagliptin and a similar total daily dose of metformin once daily  
Do not exceed total daily dose of linagliptin 5 mg and metformin 2000 mg | Take with a meal | 2.5/1,000 mg, 5/1,000 mg tablets |
| saxagliptin (Onglyza)             | 2.5 to 5 mg daily by mouth                         | Take with or without food                  | 2.5 mg, 5 mg tablets          |
| saxagliptin/ metformin ER (Kombiglyze XR) | 1 tablet daily; maximum per day: 5 mg saxagliptin, 2,000 mg metformin | Take with evening meal                    | 2.5/1,000 mg, 5/500 mg, 5/1,000 mg tablets |
| sitagliptin (Januvia)             | 100 mg once daily by mouth                         | Take with or without food                  | 25 mg, 50 mg, 100 mg tablets  |
| sitagliptin/ metformin (Janumet)  | 1 tablet twice daily by mouth maximum per day: 100 mg sitagliptin, 2,000 mg metformin | Take with food  
Do not split, crush, or chew tablets | 50/500 mg, 50/1,000 mg tablets |
| sitagliptin/ metformin ER (Janumet XR) | Dosage based on patient’s current sitagliptin and/or metformin regimens up to a maximum of 100 mg sitagliptin and 2,000 mg metformin daily  
In patients not currently on metformin: 100 mg sitagliptin and 1,000 mg metformin ER per day  
In patients already treated with metformin, the recommended starting dose is sitagliptin 100 mg and the previous total daily dose of metformin  
In patients taking metformin immediate-release 850 or 1,000 mg twice daily, the starting dose is two 50 mg sitagliptin/1,000 mg metformin ER tablets taken together once daily | Once daily with a meal preferably in the evening | 50/500 mg, 50/1,000 mg, 100/1,000 mg tablets |
### Dosages (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Time of Administration Related to Mealtime</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GLP-1 Receptor Agonists</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>albiglutide (Tanzeum)</td>
<td>30 mg SC injection once weekly; may increase to 50 mg once weekly as needed for glycemic control</td>
<td>Administer at any time of day without regard to meals Administer on the same day each week</td>
<td>30 mg, 50 mg single-dose pens</td>
</tr>
<tr>
<td>dulaglutide (Trulicity)</td>
<td>0.75 mg SC once weekly; may increase to a maximum of 1.5 mg once weekly</td>
<td>Administer at any time of day without regard to meals</td>
<td>0.75 mg/0.5 mL and 1.5 mg/0.5 mL single-dose pens</td>
</tr>
<tr>
<td>exenatide (Byetta)</td>
<td>5 mcg SC injection twice daily; dose can be increased to 10 mcg twice daily after 1 month</td>
<td>Administer at any time within the 60-minute period before the morning and evening meals preferably at least 6 hours apart</td>
<td>1.2 mL (5 mcg/dose), 2.4 mL (10 mcg/dose) prefilled pen containing 250 mcg/mL solution</td>
</tr>
<tr>
<td>exenatide ER (Bydureon)</td>
<td>2 mg SC injection administered once weekly</td>
<td>Administer at any time without regard to meals</td>
<td>2 mg vial containing powdered exenatide with a 0.65 mL prefilled syringe containing diluents; 2 mg single-dose pen</td>
</tr>
<tr>
<td>liraglutide (Victoza)</td>
<td>0.6 mg once daily SC injection into the upper arm, thigh, or abdomen for 1 week Dose may be increased to 1.2 mg once daily SC injection; maximum dose is 1.8 mg daily</td>
<td>Administer once daily at any time of day independent of meals</td>
<td>Prefilled multidose pens that deliver 0.6 mg, 1.2 mg, and 1.8 mg doses; Pens contain 6 mg/mL (3 mL)</td>
</tr>
<tr>
<td>liraglutide/insulin degludec (Xultophy)</td>
<td>16 units SC once daily Do not exceed 50 units (50 units liraglutide and 1.8 mg insulin degludec) per day</td>
<td>Administer at the same time each day with or without food.</td>
<td>Prefilled multidose pen that delivers 10 to 50 units/injection Pen contains 3.6 mg/mL liraglutide and 100 units/mL insulin degludec (3 mL)</td>
</tr>
<tr>
<td>lixisenatide (Adlyxin)</td>
<td>10 mcg once daily SC for 14 days on day 15 increase to 20 mcg once daily</td>
<td>Administer once daily within 1 hour before the first meal of the day</td>
<td>Prefilled multidose pens that deliver 10 or 20 mcg/dose Pens contain 50 mcg/mL (starter pen) and 100 mcg/mL (maintenance pen) (3 mL)</td>
</tr>
<tr>
<td>lixisenatide/insulin glargine (Soliqua)</td>
<td>Initial dose in patients not controlled on &lt; 30 units of basal insulin or on lixisenatide is 15 units SC once daily Initial dose in patients not controlled on 30-60 units of basal insulin is 30 units SC once daily. Do not exceed 60 units per day (20 mcg lixisenatide/60 units insulin glargine)</td>
<td>Administer once daily within 1 hour before the first meal of the day</td>
<td>Prefilled multidose pen that deliver 15 to 60 units per dose Pen contains lixisenatide 33 mcg and insulin glargine 100 units per mL (3 mL)</td>
</tr>
</tbody>
</table>
All GLP-1 agonist products should be kept refrigerated (36°F to 46°F). The manufacturers recommend that, after first use, exenatide (Byetta) can be kept at temperature not to exceed 77°F, for up to 30 days if needed; after first use, liraglutide (Victoza), and lixisenatide (Adlyxin) can be kept at room temperature, not to exceed 86°F, for up to 30 days, if needed; liraglutide/insulin degludec (Xultophy) can be kept at room temperature, not to exceed 86°F, for up to 21 days; dulaglutide (Trulicity) and lixisenatide/insulin glargine (Soliqua) can be kept at room temperature, not to exceed 86°F, for up to 14 days; and exenatide ER (Bydureon) may be kept at room temperature not to exceed 77°F for up to 4 weeks, if needed.

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

Patients with eGFR < 45 mL/min/1.73m² should receive saxagliptin 2.5 mg once daily.

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 (CrCl < 30 mg/min) or ESRD on dialysis, the recommended daily dose of sitagliptin is 25 mg.

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

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

Doses of albiglutide (Tanzeum), dulaglutide (Trulicity), exenatide (Byetta, Bydureon), liraglutide (Victoza), lixisenatide (Adlyxin), liraglutide/insulin degludec (Xultophy), and lixisenatide/insulin glargine (Soliqua) should be injected in the thigh, abdomen, or upper arm, rotating sites regularly.

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

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

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

Alogliptin/metformin, alogliptin/pioglitazone, linagliptin/metformin ER (Jentadueto XR), saxagliptin/metformin ER (Kombiglyze XR), and sitagliptin/metformin ER tablets should be swallowed whole and never crushed, cut, or chewed.

Patients who require < 15 units or > 60 units of lixisenatide/insulin glargine (Soliqua) should be prescribed an alternative antidiabetic agent. Similarly, patients who require < 16 units or > 50 units liraglutide/insulin degludec (Xultophy) should be prescribed an alternative antidiabetic product. Do not split the dose or mix either product with other insulins. If a dose of either agent is missed, therapy should be resumed with the next scheduled dose at the prescribed dosage.
When an iodinated contrast imaging, including intra-arterial, procedure is required, discontinue metformin-containing products (Kazano, Janumet, Janumet XR, Jentadueto, Jentadueto XR, Kombiglyze XR) at the time of, or prior to the procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m²; or in patients with a history of liver disease, alcoholism, or heart failure. Reassess eGFR 48 hours after the procedure; linagliptin/metformin may be restarted if renal function is stable.

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

**CLINICAL TRIALS**

**Search Strategies**

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

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

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

**pramlintide (Symlin)**

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

A 29-week, double-blind, placebo-controlled study randomized 296 patients with T1DM to pramlintide or placebo as an adjunct to insulin. Insulin use was adjusted as needed. Baseline HbA1c was 8.1% for both groups. At week 29, HbA1c reductions were similar for both study arms (both -0.5%). Pramlintide treatment significantly reduced postprandial glucose excursions (p<0.0005) and weight (pramlintide -1.3 ± 0.30 kg; placebo +1.2 ± 0.30 kg; p<0.0001). At week 29, insulin dose decreased by 28% and 4% in pramlintide- and placebo-treated groups, respectively. Nausea was reported by 63% and 36% of patients in pramlintide and placebo groups (p<0.01), respectively, and severe hypoglycemia rates were 0.57 for pramlintide and 0.30 for placebo (event rate/patient-year; p<0.05).

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

**DPP-4 Inhibitors**

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

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

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

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

**alogliptin/metformin (Kazano) versus metformin**

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

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

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

**alogliptin plus pioglitazone/metformin versus pioglitazone/metformin**

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

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

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

**alogliptin (Nesina) and cardiovascular risk**

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

In 2 double-blind, multicenter trials (n>350 evaluable patients/trial) in adult patients with inadequately controlled T2DM, oral linagliptin monotherapy was significantly more effective than placebo in improving glycemic control with placebo-corrected adjusted mean changes in HbA1c levels of -0.69% to -0.88% after 12 or 24 weeks. Linagliptin was generally well tolerated in clinical trials, having neutral or minimal effects on bodyweight and generally being associated with a very low incidence of hypoglycemia. 193

A multi-center, 24-week randomized, double-blind, parallel group study in 1,058 patients comparing linagliptin and placebo when added to metformin plus sulfonylurea in persons with T2DM inadequately controlled (HbA1c of 7% to 10%) by metformin plus sulfonylurea. 194 At week 24, the linagliptin placebo-corrected HbA1c adjusted mean change from baseline was -0.62% (p<0.0001). Fasting plasma glucose was reduced with linagliptin relative to placebo (-0.7 mmol/L, 95% CI -1 to -0.4; p<0.0001). Symptomatic hypoglycemia occurred in 16.7% and 10.3% of the linagliptin and placebo groups, respectively. Hypoglycemia was generally mild or moderate; severe hypoglycemia was reported in 2.7% and 4.8% of the participants experiencing hypoglycemic episodes in the linagliptin and placebo arms, respectively. No significant weight changes were noted.

In a 24-week study, patients with T2DM were randomized to receive the initial combination of 30 mg pioglitazone plus 5 mg linagliptin (n = 259) or pioglitazone plus placebo (n = 130). 195 The primary endpoint of change from baseline in HbA1c with the initial combination of linagliptin plus pioglitazone was -1.06% compared with -0.56% for placebo plus pioglitazone (95% CI -0.71, -0.3; p<0.0001). Reductions in FPG were significantly greater for linagliptin plus pioglitazone than with placebo plus pioglitazone; -1.8 and -1 mmol/L, respectively, (95% CI -1.2, -0.4; p<0.0001). Patients taking linagliptin plus pioglitazone, compared with those receiving placebo plus pioglitazone, were more likely to achieve HbA1c < 7% (42.9% versus 30.5%, respectively; p=0.0051) and reduction in HbA1c of at least 0.5% (75% versus 50.8%, respectively; p<0.0001). Hypoglycemic episodes, all mild in severity, occurred in 1.2% of the linagliptin plus pioglitazone patients and none in the placebo plus pioglitazone group.

In a phase III, double-blind, placebo-controlled trial, patients with inadequately controlled T2DM on sulfonylurea monotherapy were randomly assigned to receive treatment with linagliptin 5 mg once daily or placebo as adjunctive therapy to sulfonylurea therapy. 196 Mean baseline characteristics were similar in the linagliptin and placebo groups. Linagliptin treatment was associated with a placebo-corrected mean (95% CI) change in HbA1c from baseline to 18 weeks of -0.47% (p<0.0001). Patients in the linagliptin group were more likely to achieve the HbA1c target level of <7% after 18 weeks of treatment (15.2% versus 3.7%, respectively; odds ratio [OR] = 6.5; 95% CI, 1.7-24.8; p=0.007). The overall frequency of adverse events was similar between the linagliptin and placebo groups, including incidences of hypoglycemia, and none of the hypoglycemic episodes were assessed as severe by the investigator. Changes in mean body weight was similar in both groups (p=0.12).

**linagliptin/empagliflozin (Glyxambi)**

A double-blind, randomized, active-controlled study compared the safety and efficacy of linagliptin 5 mg in combination with empagliflozin 10 mg or 25 mg to the individual components in 686 patients with T2DM. 197 After a 2-week run-in period, patients who were inadequately controlled on at least 1,500 mg of metformin daily were randomized 1:1:1:1:1 to empagliflozin 10 mg, empagliflozin 25 mg, linagliptin 5 mg, linagliptin 5 mg/empagliflozin 10 mg, or linagliptin 5 mg/empagliflozin 25 mg. At week
24, the fixed dose linagliptin/empagliflozin combinations provided statistically significant improvements in HbA1c (p<0.0001) and FPG (p<0.001) compared to the individual components. The combination treatment also resulted in a statistically significant reduction in body weight compared to linagliptin (p<0.0001); however, no statistically significant differences in body weight were seen when compared to empagliflozin alone.

**linagliptin/metformin (Jentadueto)**

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

A 24-week randomized, double-blind, placebo-controlled factorial study involving 791 patients was performed to determine the efficacy of linagliptin as initial therapy with metformin.198 Patients (52%) entering the study already on antihyperglycemic therapy went through a 4-week wash-out period followed by a 2-week placebo run-in period. Patients who had inadequate glycemic control (HbA1c ≥ 7% and ≤ 10.5%) were randomized into the study. Forty-eight percent of patients entering the study were not taking an antihyperglycemic and went straight into the 2-week placebo run-in phase. Patients who had inadequate glycemic control (HbA1c ≥ 7.5% and < 11%) after the 2-week placebo run-in phase were randomized into the study. Randomization was stratified by baseline HbA1c (< 8.5% versus ≥ 8.5%) and prior use of an antihyperglycemic medication. Patients were randomized in a 1:2:2:2:2:2 ratio to either placebo or 1 of the 5 treatment arms (linagliptin 5 mg once daily; metformin 500 mg twice daily; linagliptin 2.5 mg twice daily plus metformin 500 mg twice daily; metformin 1000 mg twice daily; and linagliptin 2.5 mg twice daily plus metformin 1,000 mg twice daily). Initial therapy with the combination of linagliptin and metformin significantly improved HbA1c levels (change from baseline of -1.2 for linagliptin 2.5 mg/metformin 500 mg twice daily and -1.6 for linagliptin 2.5 mg/metformin 1,000 mg twice daily) compared to linagliptin monotherapy (change from baseline of -0.5), metformin monotherapy (change from baseline of -0.6 for metformin 500 mg twice daily and -1.1 for metformin 1000 mg twice daily), and placebo (change from baseline of 0.1), CI= 95%. The FPG also improved with linagliptin plus metformin (change from baseline of -33 mg/dL for linagliptin 2.5 mg/metformin 500 mg twice daily and -49 mg/dL for linagliptin 2.5 mg/metformin 1,000 mg twice daily) compared to linagliptin monotherapy (change from baseline of -9 mg/dL), metformin monotherapy (change from baseline of -16 mg/dL for metformin 500 mg twice daily and -32mg/dL for metformin 1,000 mg twice daily), and placebo (change from baseline of 10 mg/dL), CI= 95% and p<0.0001.

A 104-week double-blind, glimepiride-controlled, non-inferiority study was performed in patients with T2DM with insufficient glycemic control despite being on metformin compared to patients having coadministration of linagliptin plus metformin.199 Patients on metformin monotherapy had a run-in period of 2 weeks and patients taking metformin with another oral antihyperglycemic had a metformin monotherapy (daily dose at least 1,500 mg) run-in period of 6 weeks and washout of the other antihyperglycemic agent. After an additional 2-week placebo run-in period, patients with poor glycemic control (HbA1c 6.5% to 10%) were randomized 1:1 to the addition of linagliptin 5 mg daily (n = 766) or glimepiride (n = 761, initial dose 1 mg per day and titrated up to 4 mg per day as needed over 12 weeks). After 52 weeks, both groups, linagliptin plus metformin and glimepiride plus metformin, saw a decrease in HbA1c and FPG levels, -0.4% and -0.6% (CI 97.5%) and -9 mg/dL and -16 mg/dL.
respectively. The incidence of hypoglycemia was lower in the linagliptin plus metformin group compared to the glimepiride plus metformin group, 5.4% and 31.8%, respectively (p< 0.0001). Patients treated with linagliptin plus metformin experienced a significant decrease from baseline body weight compared to a significant weight gain in the glimepiride plus metformin group (-1.1 kg versus +1.4 kg, p<0.0001).

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

**linagliptin/metformin ER (Jentadueto XR)**

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

**saxagliptin (Onglyza)**

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

A randomized, 24-week, phase III, double-blind trial evaluated the efficacy and safety of saxagliptin added to a submaximal sulfonylurea dose in comparison to up titration of sulfonylurea monotherapy in patients with T2DM taking sulfonylurea monotherapy with inadequate glycemic control. Initially, all patients received open-label glyburide 7.5 mg daily for 4 weeks. A total of 768 patients between 18 to 77 years of age with HbA1c screening value of 7.5% to 10% were randomized and treated with saxagliptin 2.5 or 5 mg in combination with glyburide 7.5 mg versus glyburide 10 mg monotherapy for
24 weeks. Blinded up titration glyburide was allowed in the glyburide-only arm to a maximum total daily dose of 15 mg. Results at 24 weeks indicated that 92% of glyburide-only patients were up titrated to a total daily glyburide dose of 15 mg. Saxagliptin 2.5 and 5 mg provided statistically significant adjusted mean decreases from baseline to week 24 versus up titrated glyburide in HbA1c (-0.54%, -0.64% versus +0.08%, respectively; both p<0.0001) and fasting plasma glucose (-7, -10 versus +1 mg/dL, respectively; p=0.0218 and p=0.002). The proportion of patients achieving an HbA1c <7% was greater for saxagliptin 2.5 mg and 5 mg versus up titrated glyburide (22.4% and 22.8% versus 9.1%, respectively; both p<0.0001). Postprandial glucose area under the curve was reduced for saxagliptin 2.5 and 5 mg versus up titrated glyburide (both p<0.0001). Adverse event occurrence was similar across all groups. Reported hypoglycemic events were not statistically significantly different for saxagliptin 2.5 and 5 mg versus up titrated glyburide (13.3% and 14.6% versus 10.1%, respectively).

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

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

The efficacy and safety of saxagliptin plus a TZD in 565 patients with T2DM and inadequate glycemic control on TZD monotherapy were evaluated in a multicenter, randomized, double-blind, phase 3 study. Patients had a baseline HbA1c of 7% to 10.5% while on pioglitazone 30 or 45 mg or rosiglitazone 4 mg or 8 mg for at least 12 weeks before screening. Patients were given saxagliptin 2.5 or 5 mg once daily or placebo plus a stable TZD dose for 24 weeks. The adjusted mean decreases in HbA1c versus placebo from baseline to week 24, the primary outcome parameter, was -0.66% (p=0.0007) for saxagliptin 2.5 mg and -0.94% (p<0.0001) for saxagliptin 5 mg compared to -0.3% with placebo. The percentage of patients achieving HbA1c <7% was 42.2% (p=0.001), 41.8% (p=0.0013), and 25.6% for saxagliptin 2.5 mg plus TZD, 5 mg plus TZD, and placebo groups, respectively. Hypoglycemic events were similar across all groups.

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

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

**saxagliptin (Onglyza) and cardiovascular risk**

The SAVOR TIMI-53 study, a randomized, double-blind, placebo-controlled phase 4, manufacturer-funded trial, evaluated CV outcomes with saxagliptin (5 mg daily or 2.5 mg daily in patients with an estimated glomerular filtration rate [eGFR] ≤ 50 mL/minute).

209 Patients (n = 16,492) were followed for a mean of 2.1 years. The study found that, in patients with T2DM with a history of or at risk for CV events, saxagliptin had no effect on the primary efficacy endpoint of a composite of CV death, myocardial infarction (MI), or ischemic stroke (hazard ratio [HR] with saxagliptin, 1; 95% CI, 0.89 to 1.12; p=0.99 for superiority; p<0.001 for noninferiority). The study did show that the rate of hospitalization for heart failure (HF) was significantly increased (p=0.007) with saxagliptin. The study authors recommend further investigation of this increased rate of HF. Rates of adjudicated cases of acute and chronic pancreatitis were similar.

**saxagliptin/metformin ER (Kombiglyze XR)**

No large scale clinical efficacy or safety studies have been conducted specifically with the fixed-dose combination of saxagliptin and metformin ER. The FDA approved once-daily saxagliptin and metformin ER based upon 2 phase 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. Studies found that the 10 mg daily dose of saxagliptin does not provide greater efficacy than the 5 mg daily dose.

**sitagliptin (Januvia)**

The efficacy and safety of sitagliptin were evaluated in a randomized, double-blind study with 701 patients with T2DM who were on metformin and evaluated for 24 weeks.210 Patients had a baseline HbA1c ≥7% to ≤ 10% and were on metformin 1,500 mg daily or more. Sitagliptin 100 mg daily or placebo was added. After 24 weeks, HbA1c were reduced by -0.65% by sitagliptin. Significantly more patients on sitagliptin (47%) achieved HbA1c of <7% compared to placebo (18.3%). Body weight decreased similarly in both groups. Sitagliptin was well tolerated. Another study of similar design with sitagliptin added to ongoing metformin therapy demonstrated similar reductions of HbA1c.211

**sitagliptin (Januvia) and cardiovascular risks**

TECOS was a double-blind, evaluated the CV outcomes for sitagliptin in 14,671 patients with T2DM and CV disease.212 Patients were randomized to sitagliptin 100 mg daily (or 50 mg daily if eGFR was ≥ 30 and < 50 mL/min/1.73m²) or placebo.213 After a median follow up of 3 years, the primary composite endpoint (CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina) occurred at similar rates (11.4% and 11.6%, respectively). A subanalysis revealed a similar finding for the primary composite outcome in 2,004 patients ≥ 75 years of age (HR, 1.10; [0.89 to 1.36]), death (HR, 1.05 [0.83 to 1.32]), HF hospitalization (HR, 0.99; [0.65 to 1.49]), or severe hypoglycemia (HR, 1.03; [0.62 to 1.71]).
**sitagliptin (Januvia), sitagliptin/metformin (Janumet) versus sitagliptin/metformin ER (Janumet XR)**

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

In a 24-week, double-blind, placebo-controlled, parallel-group study, 1,091 patients with T2DM and HbA1c 7.5% to 11% were randomized to sitagliptin 100 mg/metformin 1,000 mg, sitagliptin 100 mg/metformin 2,000 mg, metformin 1,000 mg immediate-release, or metformin 2,000 mg immediate-release in divided doses twice daily, sitagliptin 100 mg daily, or placebo.\(^{214}\) The mean baseline HbA1c was 8.8%. The placebo-subtracted HbA1c changes from baseline were -2.07% (sitagliptin/metformin 2,000 mg), -1.57% (sitagliptin/metformin 1,000 mg), -1.30% (metformin 2,000 mg), -0.99% (metformin 1,000 mg), and -0.83% (sitagliptin 100 mg) (p<0.001 for comparisons versus placebo and for coadministration versus respective monotherapies). The percentage of patients achieving HbA1c <7% was 66% for sitagliptin/metformin 2,000 mg group (p<0.001 versus sitagliptin monotherapy and metformin 2,000 mg groups). The incidence of hypoglycemia was low (0.5% to 2.2%) across active treatment groups and not significantly different from that in the placebo group (0.6%).

**sitagliptin (Januvia) versus saxagliptin (Onglyza)**

Adult patients with T2DM (n = 801) and an HbA1c of 6.5% to 10% on stable metformin doses (1,500-3,000 mg/day) were randomized to add-on saxagliptin 5 mg or sitagliptin 100 mg once daily for 18 weeks.\(^{215}\) The adjusted mean changes in HbA1c following the addition of saxagliptin or sitagliptin to stable metformin therapy were -0.52% and -0.62%, respectively. The between-group difference was 0.09% (95% CI, -0.01 to 0.20%), demonstrating noninferiority as defined as an upper limit of the 2-sided 95% CI of the HbA1c difference between treatments was <0.3%). Both treatments were generally well tolerated; incidence and types of adverse events were comparable between groups. Hypoglycemic events, mostly mild, were reported in approximately 3% of patients in each treatment group. Body weight declined by a mean of 0.4 kg in both groups.

**sitagliptin (Januvia) versus glipizide (Glucotrol\(^\text{®}\))**

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.\(^{216}\) From a mean baseline HbA1c of 7.5%, changes from baseline were -0.67% at week 52 in both groups, confirming noninferiority. The proportions of patients achieving an HbA1c <7% were 63% (for sitagliptin) and 59% (for glipizide). The proportion of patients experiencing hypoglycemia was significantly higher with glipizide than with sitagliptin (32% versus 5%; p<0.001). Sitagliptin led to weight loss (-1.5 kg) compared with weight gain (+1.1 kg) with glipizide (p<0.001).
sitagliptin (Januvia) 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.\textsuperscript{217} Change in HbA1c from baseline was the primary endpoint. After 18 weeks, both active add-on therapies led to greater improvements in HbA1c from the mean 7.7% baseline: -0.73% for sitagliptin (p<0.001 versus placebo) and -0.79% for rosiglitazone compared with -0.22% for placebo (p<0.001 versus placebo for both). No significant difference was observed between the sitagliptin and rosiglitazone treatments (0.06%, 95% CI, -0.14 to 0.25). The percentage of patients achieving HbA1c <7% was 55% with sitagliptin, 63% with rosiglitazone, and 38% for placebo. Body weight increased from baseline with rosiglitazone (1.5 kg) compared with a reduction in weight with sitagliptin (-0.4 kg) and placebo (-0.9 kg). The difference in body weight between the sitagliptin and rosiglitazone groups was 1.9 kg (95% CI, 1.3-2.5), and the proportion of patients experiencing a >3 kg increase in body weight was 21% in the rosiglitazone group compared with 2% in both the sitagliptin and placebo groups. Both active treatments were generally well tolerated, with no increased risk of hypoglycemia or gastrointestinal adverse events compared with placebo.

The efficacy and tolerability of sitagliptin added to pioglitazone (Actos\textsuperscript{®}) therapy were assessed in patients with T2DM and HbA1c >7% and <10% while receiving a stable dose of pioglitazone of 30 to 45 mg per day.\textsuperscript{218} In a multicenter, randomized, double-blind, placebo-controlled, parallel-group study, patients (n = 353) were randomized to receive sitagliptin 100 mg daily or placebo for 24 weeks. The primary efficacy endpoint was change from baseline in HbA1c at week 24. Mean baseline HbA1c was 8.1% in the sitagliptin group and 8% in the placebo group. After 24 weeks, sitagliptin added to pioglitazone therapy was associated with significant reductions in HbA1c (-0.70%; p<0.001) and fasting plasma glucose (FPG) (-17.7 mg/dL; p<0.001) compared with placebo. Mean HbA1c values at study endpoint were 7.2% and 7.8% in the sitagliptin and placebo groups, respectively, and the proportions of patients reaching a target HbA1c of <7% were 45.4% and 23%, respectively (p<0.001). Sitagliptin was generally well tolerated, with no increased risk of hypoglycemia compared with placebo.

**sitagliptin/metformin (Janumet) versus metformin**

In a 24-week, randomized, double-blind, placebo-controlled study, 701 patients with T2DM participated to compare sitagliptin/metformin to metformin alone.\textsuperscript{219,220} Patients already on metformin 1,500 mg per day or higher (n = 431) were randomized after completing a 2-week, single-blind placebo run-in period. Patients on metformin and another antihyperglycemic agent (n = 229) and patients not on any antihyperglycemic agents (off therapy for at least 8 weeks, n = 41) were randomized after a run-in period of approximately 10 weeks of metformin monotherapy (at a dose of at least 1,500 mg per day). Patients were randomized to also receive either 100 mg of sitagliptin or placebo, administered once daily. Mean baseline HbA1c was 8% in both groups. HbA1c changes from baseline were -0.7% for sitagliptin/metformin and zero percent for placebo/metformin. The percentage of patients achieving a HbA1c <7% was 47% in the sitagliptin/metformin immediate-release group compared to 18% in the metformin immediate-release monotherapy group.
sitagliptin/metformin + rosiglitazone (Janumet + Avandia®) versus metformin + rosiglitazone (Avandia)

In a randomized, double-blind, placebo-controlled study, 278 patients with T2DM participated in a comparison of sitagliptin in combination with metformin and rosiglitazone. 221,222 Patients on dual therapy with metformin ≥1,500 mg/day and rosiglitazone ≥4 mg/day or with metformin ≥1,500 mg/day and pioglitazone ≥30 mg/day (switched to rosiglitazone ≥4 mg/day) entered a dose-stable run-in period of 6 weeks. Patients on other dual therapy were switched to metformin ≥1,500 mg/day and rosiglitazone ≥4 mg/day in a dose titration/stabilization run-in period of up to 20 weeks in duration. After the run-in period, patients with inadequate glycemic control (HbA1C 7.5% to 11%) were randomized 2:1 to the addition of either 100 mg of sitagliptin or placebo, administered once daily. Mean reduction in HbA1C at week 54 was 1% for patients treated with sitagliptin and -0.3% for patients treated with placebo.

GLP-1 Agonists

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 T2DM inadequately controlled on ≥ 1,500 mg daily of metformin. Albiglutide 30 mg SC weekly with optional uptitration to 50 mg SC weekly after at least 4 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 the albiglutide arm and the glimepiride arm 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 ≥ 30 mg daily of pioglitazone (with or without ≥ 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 ≥ 1,500 mg daily of metformin and glimepiride 4 mg daily. Patients were randomized to receive albiglutide 30 mg SC weekly with optional up titration to 50 mg weekly after at least 4 weeks, placebo, or pioglitazone 30 mg daily with optional up titration 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%; difference of 0.25 with CI of 0.1 to 0.4). 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 up titration 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 ≥ 1,500 mg daily of metformin (with or without sulfonylurea). Patients were randomized to receive albiglutide 30 mg SC weekly with optional up titration 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 up titrated 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 up titration 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% 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 ≥ 6.5% and ≤ 9.5%) with diet and exercise with or without 1 anti-diabetic agent used at submaximal dose.\(^{223,224}\) Patients were randomized to dulaglutide 1.5 mg or 0.75 mg once weekly or metformin 1,500 to 2,000 mg/day. Other oral hypoglycemic agents were discontinued prior to lead-in period. Primary endpoint was change in HbA1c at week 26. Mean changes in HbA1c of -0.8%, -0.7% and -0.6% were reported for dulaglutide 1.5 mg and 0.75 mg and metformin, respectively. Dulaglutide 1.5 and 0.75 mg were considered superior to metformin (p<0.025 for both). A greater percentage of patients on dulaglutide reached HbA1c < 7% and ≤ 6.5% compared to metformin (p < 0.05 for all comparisons). No severe hypoglycemia was reported. Mean changes in body weight were similar across all groups. Nausea, vomiting, and diarrhea were common adverse effects, with similar incidence reported between dulaglutide and metformin.

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

AWARD-5: A 104-week placebo-controlled, double-blind, parallel-arm study randomized 1,098 patients to dulaglutide 1.5 mg or 0.75 mg once weekly, sitagliptin 100 mg/day, or placebo, all as add-on to metformin in patients with T2DM.\(^{225}\) Primary endpoint was change in HbA1c at 52 weeks. The mean HbA1c changes were -1.10%, -0.87 %, and -0.39% for dulaglutide 1.5 mg, dulaglutide 0.75 mg, and sitagliptin, respectively (p < 0.001, both comparisons). No events of severe hypoglycemia were reported. Mean weight changes at 52 weeks were greater with dulaglutide 1.5 mg (-3.03 kg) and dulaglutide 0.75 mg (-2.60 kg) compared with sitagliptin (-1.53 kg) (p < 0.001, both comparisons).

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

AWARD-1: This 52-week, placebo-controlled, parallel-arm study compared of the effects of dulaglutide and exenatide on glycemic control in 976 patients with T2DM not adequately controlled with metformin and pioglitazone.\(^{226,227}\) Patients were randomized to dulaglutide 1.5 mg or 0.75 mg, exenatide 10 mcg twice daily, or placebo. Patients were also on metformin ≥ 1,500 mg/day and pioglitazone 30 to 45 mg/day. Treatment groups were open-label for exenatide, while all others were blinded. After 26 weeks, patients in the placebo treatment group were randomized to either dulaglutide 1.5 mg or 0.75 mg once weekly. Primary endpoint was change in HbA1c at week 26. Mean reduction in HbA1c was 1.5%, 1.3%, 1%, and 0.5% for dulaglutide 1.5 mg and 0.75 mg, exenatide and placebo, respectively (p<0.01 for all as compared to placebo). A greater percentage of patients achieved HbA1c < 7% with both dulaglutide doses than with exenatide or placebo (all p<0.001). At both time points of 26 and 52 weeks, incidence of hypoglycemia was reported less in patients receiving dulaglutide 1.5 mg as compared to exenatide. While both doses of dulaglutide resulted in weight loss, compared to placebo, the difference in weight as compared to exenatide was -0.2 kg for dulaglutide 1.5 mg and +1.3 kg for dulaglutide 0.75 mg.

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

AWARD-2: In a 78-week, open-label study effects on glycemic control in patients with T2DM of dulaglutide were compared with insulin glargine. Patients (n = 807) were randomized to dulaglutide 1.5 mg or 0.75 mg once weekly, or insulin glargine once daily, all as add-on to maximally tolerated doses of metformin and glimepiride. Dosages of insulin glargine were initiated at 10 units once daily and titrated to a target fasting glucose of < 100 mg/dL. Only 24% of patients on insulin glargine were...
titrated to goal at the 52-week primary endpoint. The dosage of insulin glargine could be reduced or discontinued if persistent hypoglycemia occurred. At 52 weeks, reductions in HbA1c were 1.1%, 0.8%, and 0.6% for dulaglutide 1.5 mg and 0.75 mg, and insulin glargine, respectively. Dulaglutide resulted in an overall weight loss, while insulin glargine resulted in a weight gain. Mean difference in body weight as compared to insulin glargine was -1.9 kg for dulaglutide 1.5 mg and -1.3 kg for dulaglutide 0.75 mg.

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

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

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

AWARD-6: In this open-label, parallel-arm study the efficacy of dulaglutide was compared to liraglutide in 599 patients with T2DM who were also on metformin. 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) as add-on to sulfonylurea**

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

A double-blind, placebo-controlled study of 733 patients with T2DM and inadequate glycemic control with combined metformin-sulfonylurea therapy, found comparable results at 30 weeks using the same treatment arms as the above study.\(^{232}\) At week 30, HbA1c changes from baseline were -0.8% (exenatide 10 mcg), -0.6% (exenatide 5 mcg), and +0.2% (placebo, adjusted p<0.0001 versus placebo). Placebo-adjusted reductions were -1% for exenatide 10 mcg and -0.8% for exenatide 5 mcg groups. In the evaluable population, exenatide-treated patients were more likely to achieve HbA1c ≤ 7% than placebo-treated patients (34%, exenatide 10 mcg group; 27%, exenatide 5 mcg group; and 9%, placebo; p<0.0001). Weight loss occurred in both exenatide treated groups (-1.6 kg, p≤0.01 versus placebo). Mild or moderate nausea was the most frequently reported adverse event. Hypoglycemia was reported in 28% of exenatide 10 mcg group, 19% of exenatide 5 mcg group, and 13% of the placebo group.

**exenatide ER (Bydureon) versus exenatide (Byetta)**

DURATION-1\(^{233}\): 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 T2DM (HbA1c 8.3%, mean fasting plasma glucose 9 mmol/L, and weight 102 kg [SD 20]). The patients were naïve to drug therapy, or on 1 or more oral antidiabetic agents. The primary endpoint was the change in HbA1c at 30 weeks. Patients on exenatide once a week had significantly greater changes in HbA1c than patients on exenatide twice a day (-1.9 versus -1.5, 95% CI -0.54 to -0.12; p=0.0023). More patients on the once a week agent versus twice a day achieved target HbA1c levels of 7% or less (77% once weekly exenatide versus 61% twice daily exenatide, p=0.0039). In an open-label extension of the DURATION 1 study, 258 patients either continued or were switched to exenatide ER 2 mg once weekly for an additional 22 weeks.\(^{234}\) Patients that continued exenatide ER maintained HbA1c through 52 weeks (-2.0% [-2.1 to -1.8%], LS mean [95%CI]). Patients that switched from twice daily exenatide to weekly exenatide ER experienced further reductions in HbA1c; however, both groups reported the same HbA1c reduction and mean HbA1c at week 52. There was no increased risk of hypoglycemia and similar reductions in body weight reported with exenatide ER. In addition, in 153 patients who completed 5 years of treatment, HbA1c remained significantly reduced compared to baseline and no new safety signals were observed with once weekly exenatide treatment.\(^{235}\)

DURATION-5\(^{236,237}\): A 24-week, randomized, open-label trial compared the safety and efficacy of exenatide extended-release (ER) 2 mg weekly to exenatide 10 mcg twice daily in addition to existing oral antidiabetic agents. Subjects (n = 252) included patients with T2DM and inadequate glycemic control with diet and exercise alone or with oral antidiabetic therapy, including metformin, a sulfonylurea, a thiazolidinedione, or combination of 2 of those therapies. The mean baseline HbA1c was 8.4%. The mean change in HbA1c (%) at week 24 was -1.6 for exenatide ER and -0.9 for exenatide. Adverse reactions reported were nausea, diarrhea, and injection site erythema in 14, 9.3, and 5.4% of subjects treated with exenatide ER, respectively and 35, 4.1, and 2.4% of subjects treated with exenatide, respectively. No major incidence of hypoglycemia was reported.
Exenatide (Byetta) and Insulin Glargine (Lantus®)

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

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

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

Exenatide ER (Bydureon) versus Liraglutide (Victoza)

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

**liraglutide (Victoza) versus glimepiride**

LEAD-3242: In this 52-week, controlled trial 746 patients with T2DM were randomized to once daily liraglutide 1.2 mg or 1.8 mg or glimepiride 8 mg. The primary outcome was change in HbA1c. HbA1c decreased by 0.51% with glimepiride versus 0.84% with liraglutide 1.2 mg (difference -0.33%; 95% CI, -0.53 to -0.13, p<0.05) and 1.14% with liraglutide 1.8 mg (difference -0.62%; 95% CI, -0.83 to -0.42, p<0.0001). No events of major hypoglycemia occurred. Five patients discontinued therapy due to vomiting in the liraglutide 1.2 mg group, 1 patient in 1.8 mg group, and 0 patients in the glimepiride group. Discontinuations due to ineffective therapy were 3.6% in the liraglutide 1.8 mg group, 6% in the liraglutide 1.2 mg group, and 10.1% in the glimepiride group. Liraglutide 1.8 and 1.2 mg resulted in 2.5 and 2.1 kg weight loss, respectively (p<0.0001) compared to a 1.1 kg weight gain with glimepiride.

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

LEAD-2243: A 26-week controlled trial randomized 1,091 patients to liraglutide 0.6 mg, 1.2 mg, 1.8 mg, placebo, or glimepiride 4 mg, all as add-on to metformin up to 2,000 mg per day. HbA1c increased by 0.1% with placebo/metformin, decreased by 1% with glimepiride/metformin, decreased by 1% in both liraglutide 1.2 mg and 1.8 mg groups (p<0.0001 for the liraglutide groups). Discontinuations due to ineffective therapy were 5.4% in the liraglutide 1.8 mg/metformin group, 3.3% in the liraglutide 1.2 mg/metformin group, 23.8% in the placebo/metformin group, and 3.7% in the glimepiride/metformin group. The liraglutide 1.8 mg/metformin and liraglutide 1.2 mg/metformin groups had a weight loss of 2.8 and 2.6 kg, respectively (p<0.05) compared to a 1.5 kg decrease in the placebo/metformin and 1 kg increase in the glimepiride/metformin groups.

**liraglutide (Victoza) versus rosiglitazone as add-on glimepiride**

LEAD-1244: This was a 26-week controlled trial of 1,041 patients randomized to liraglutide 0.6 mg, 1.2 mg, 1.8 mg, placebo, or rosiglitazone 4 mg, all as add-on to glimepiride 4 mg (the dose of glimepiride could be reduced by the investigator). Liraglutide 1.2 or 1.8 mg resulted in greater reductions in HbA1c (-1.1% each, p<0.0001), compared with placebo (+0.2%, p<0.0001) or rosiglitazone (-0.4%, p<0.0001) when added to glimepiride. Changes in body weight observed were: liraglutide 1.8 mg (-0.2 kg), liraglutide 1.2 mg (+0.3 kg), placebo (-0.1 kg), and rosiglitazone (+2.1 kg, p<0.0001). Main adverse events for all treatments were minor hypoglycemia (<10%), nausea (<11%), vomiting (<5%), and diarrhea (<8%). The percentage of patients who discontinued due to ineffective therapy was 3% in the liraglutide 1.8 mg/glimepiride group, 3.5% in the liraglutide 1.2 mg/glimepiride group, 17.5% in the placebo/glimepiride group, and 6.9% in the rosiglitazone/glimepiride group.
**liraglutide (Victoza) versus insulin glargine (Lantus) as add-on metformin and glimepiride**

LEAD-5\(^{245}\): In a 26-week study of 581 patients randomized to liraglutide 1.8 mg, placebo, or insulin glargine open-label arm (dose could be adjusted), all as add-on to metformin 2,000 mg or glimepiride 4 mg. The liraglutide group resulted in 1.3% decrease (\(p<0.0001\)) in HbA1c compared to 0.2% decrease with placebo, and 1.1% decrease in the insulin group. The difference in HbA1c for insulin glargine is within the predefined 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% nausea, were reported with liraglutide. Discontinuation percentages due to ineffective therapy were 0.9% in the liraglutide 1.8 mg group, 0.4% in the insulin glargine group, and 11.3% in the placebo group.

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

LEAD-4: This was a 26-week controlled trial of 533 patients randomized to liraglutide 1.2 mg, 1.8 mg, or placebo, all as add-on to rosiglitazone 8 mg plus metformin 2,000 mg. HbA1c significantly decreased by 1.5% in each of the liraglutide groups compared to a 0.5% decrease in the placebo group.\(^{246}\) Dose-dependent weight loss occurred with liraglutide 1.2 mg and 1.8 mg groups (1 kg and 2 kg, respectively \([p<0.0001]\)) compared with weight gain with placebo (0.6 kg). Minor hypoglycemia was reported more frequently with liraglutide, but no major hypoglycemia occurred. Gastrointestinal (GI) adverse events were more common with liraglutide; however, most GI events occurred early in therapy and were transient. Discontinuation percentages due to ineffective therapy were 1.7% in the liraglutide 1.8 mg group, 1.7% in the liraglutide 1.2 mg group, and 16.4% in the placebo group.

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

LEAD-6 versus exenatide: In a 26-week, open-label trial, 464 patients with inadequately controlled T2DM on maximally tolerated doses of metformin, sulfonylurea, or both, were stratified by previous oral antidiabetic therapy and randomized to once daily liraglutide 1.8 mg or exenatide 10 mcg twice daily.\(^{247,248}\) Patients randomized to exenatide started on a dose of 5 mcg twice-daily for 4 weeks and then were escalated to 10 mcg twice daily. Compared with exenatide, liraglutide 1.8 mg resulted in significantly greater reductions in HbA1c (-1.1% versus -0.8%; 95% CI, -0.47 to -0.18; \(p<0.0001\)) and more patients achieved an HbA1c value of < 7% (54% versus 43%, respectively; odds ratio 2.02; 95% CI, 1.31 to 3.11; \(p=0.0015\)). Liraglutide also reduced mean FPG more than exenatide (-1.61 versus -0.60 mmol/L; 95% CI, -1.37 to -0.65; \(p<0.0001\)) but PPG control was less effective after breakfast and dinner. Both drugs were well tolerated, but nausea was less persistent \((p<0.0001)\) and minor hypoglycemia \((p=0.0131)\) less frequent with liraglutide than with exenatide. Two patients taking both exenatide and a sulfonylurea had a major hypoglycemic episode. Both treatment groups had a mean decrease from baseline in body weight of approximately 3 kg.
liraglutide (Victoza) versus sitagliptin (Januvia) as add-on to metformin

In a 26-week parallel-group, open-label trial, adult subjects with T2DM who had inadequate glycemic control on metformin were randomized to receive liraglutide 1.2 mg (n = 225) or 1.8 mg (n = 221) subcutaneous once daily, or sitagliptin 100 mg oral once daily (n = 219). The primary endpoint was change in HbA1c from baseline to week 26. Mean HbA1c was reduced to a greater extent with liraglutide 1.8 mg (−1.5%, 95% CI -1.63 to -1.37) and 1.2 mg (−1.24%, -1.37 to -1.11) than sitagliptin (−0.9%, -1.03 to -0.77). Estimated mean treatment differences for liraglutide versus sitagliptin were −0.6% (95% CI -0.77 to -0.43, p<0.0001) for 1.8 mg and -0.34% (−0.51 to −0.16, p<0.0001) for 1.2 mg liraglutide. Nausea was more common with both doses of liraglutide (27% and 21%) than with sitagliptin (5%). Minor hypoglycemia was similar in all treatment groups. Participants continued their same treatment regimen in a 26-week extension study. At week 52, mean reductions in HbA1c from baseline were similar to those reported at week 26; liraglutide 1.2 mg (−1.29% [95% CI: −1.43 to −1.15]), 1.8 mg (−1.51% [−1.65 to −1.37]), and sitagliptin (−0.88% [−1.02 to −0.74]). Estimated mean treatment differences were −0.4% (95% CI −0.59 to −0.22) for liraglutide 1.2 mg versus sitagliptin and −0.63% (−0.81 to −0.44) for liraglutide 1.8 mg versus sitagliptin (p<0.0001 for both doses).

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

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

liraglutide (Victoza) and cardiovascular risks

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

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

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

A phase 3 trial compared liraglutide/insulin degludec with insulin glargine U-100, both given once daily as add-on to metformin, in patients (n = 557) inadequately controlled on insulin glargine U-100 and metformin. Starting doses were 16 units and 32 units for the combination and insulin glargine, respectively. Baseline HbA1c were 8.4% in the combination group and 8.2% in the insulin glargine group. Dosages for the combination product and the basal-insulin comparators were titrated based on FPG of 72 to 90 mg/dL. At 26 weeks, average dose for the combination was 41 units and for insulin, glargine was 66 units. HbA1c changed by -1.67% for the combination and -1.16% for insulin glargine. Percentage of patients that achieved HbA1c < 7% was 68.3% in the combination group compared to 46.2% in the insulin glargine group. Mean change in FPG was similar between groups. Treatment with liraglutide/insulin degludec was also associated with weight loss compared with weight gain with insulin glargine (-1.4 kg for degludec/liraglutide versus 1.8 kg for glargine).

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

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

The GetGoal-X trial was a randomized, open-label, parallel-group, multicenter, non-inferiority study assessing the HbA1c change with lixisenatide once daily versus exenatide twice daily in a total of 634 adults with T2DM inadequately controlled with metformin. Patients were randomized to receive either lixisenatide 20 mcg once daily (n = 318) or exenatide 10 mcg twice daily (n = 316) for 24-weeks. Lixisenatide achieved the primary efficacy objective of noninferiority to exenatide in terms of HbA1c reduction from baseline to week 24. The least squares (LS) mean change difference between the 2 groups was 0.17% (95% CI, 0.033 to 0.297), meeting a predefined noninferiority margin of 0.4%. Lixisenatide and exenatide provided comparable reductions in FPG (LS mean change difference between the 2 groups was 0.23 mmol/L [4.14 mg/dL; 95% CI, 20.052 - 0.522]). Furthermore, body weight was decreased from baseline for patients receiving each agent (LS mean change difference between the 2 groups was 1.02 kg [95%CI, 0.456 – 1.581]). The most common adverse events in both groups were gastrointestinal in nature, which occurred less frequently in the lixisenatide group as compared with the exenatide group (43.1% versus 50.6%, respectively). Symptomatic hypoglycemia also occurred less frequently in the lixisenatide group as compared with the exenatide group (2.5% versus 7.9%, respectively).

**lixisenatide (Adlyxin) and cardiovascular risks**

The ELIXA trial was a randomized, multicenter, double-blind, placebo-controlled trial designed to assess the effects of lixisenatide on CV morbidity and mortality. The trial included 6,068 patients with T2DM who experienced an acute coronary event within the last 180 days before screening. Patients were excluded who were < 30 years of age, had a percutaneous intervention within the previous 15 days, a coronary-artery bypass graft surgery for the qualifying event, planned coronary revascularization procedure within 90 days after screening, eGFR < 30 mL/min/1.73m2, a HbA1c < 5.5% or > 11%, or an inability to provide written informed consent. Eligible patients were randomized to a once-daily SC injection of lixisenatide (starting at 10 mcg daily and increased to 20 mcg daily after the first 2 weeks, at the discretion of the investigators) or placebo. The primary endpoint in the time-to-event analysis was a composite of the first occurrence of any of the following: death from CV causes, nonfatal MI, non-fatal stroke, or hospitalization for unstable angina. The primary endpoint occurred in 406 patients (13.4%) in the lixisenatide group and in 399 (13.2%) in the placebo group (HR 1.02, 95% CI, 0.89 to 1.17); the upper boundary of the 95% CI excluded 1.3 but not 1.0, which showed the noninferiority of lixisenatide to placebo (p<0.001) but not superiority (p=0.81).

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

A randomized, 30-week, active-controlled, open-label, 2-treatment arm, parallel-group study enrolled 736 patients with T2DM who had been treated with stable doses of basal insulin (15 to 40 units) for at least 6 months, with or without oral antidiabetic drugs (OADs). At screening HbA1c was between 7.5% and 10%. Patients were switched to or remained on insulin glargine U-100 during a 6-week run-in period. At the end of the run-in period, patients with an HbA1c between 7% and 10%, FPG ≤140 mg/dL, and insulin glargine daily dose of 20 to 50 units, were randomized to either combination insulin glargine/lixisenatide or insulin glargine U-100. Dosage was titrated to achieve a fasting plasma glucose (FPG) < 100 mg/dL. Maximum insulin glargine dose allowed in either group was 60 units. Target FPG was achieved in 33% of patients in both groups at 30 weeks. At 30 weeks, there was a statistically greater change in HbA1c from baseline for the combination product compared to insulin glargine.
The trial was designed to show the contribution of the GLP-1 component to glycemic lowering and the dosing algorithm was selected to isolate the effect of the GLP-1 component. At week 30, the doses of insulin glargine were the same in both groups (mean 46.7 units). More patients on the combination product achieved HbA1c <7.0% (55%) compared with 30% on insulin glargine. Mean body weight decreased by 0.7 kg with the combination and increased by 0.7 kg with insulin glargine (p<0.0001). The incidence of documented symptomatic hypoglycemia (≤70 mg/dL) was similar in both groups. Mild gastrointestinal adverse effects were very low but more frequent with the combination product.

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

Efficacy and safety of combination insulin glargine/lixisenatide were compared to the individual components in 1,170 patients with T2DM inadequately controlled on metformin, with or without a second oral antidiabetic agent.260 After a 4-week run-in to optimize metformin and stop other oral antidiabetic drugs, patients were randomized to open-label once-daily insulin glargine/lixisenatide, insulin glargine, or lixisenatide. Doses in both insulin-containing groups were titrated based on FPG <100 mg/dL to a maximum of 60 units/day. The lixisenatide group received a maximum of 20 mcg once daily. At 30 weeks, greater reductions in HbA1c from baseline were reported with the combination compared with either component alone (-1.6%, -1.3%, -0.9%, respectively). More patients achieved HbA1c <7% with the combination (74%) versus insulin glargine (59%) or lixisenatide (33%) (p<0.0001 for all). Mean change in body weight with the combination was -0.3 kg, lixisenatide -2.3 kg, and insulin glargine +1.1 kg, differences were significant. The incidence of symptomatic hypoglycemia (≤70 mg/dL) was similar with the combination and insulin glargine groups (1.4 and 1.2 events/patient-year, respectively) and lower for the lixisenatide group (0.3 events/patient-year). In addition, the combination improved postprandial glycemic control compared to insulin glargine.

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

A meta-analysis including 43 randomized (n = 19,101) controlled trials lasting at least 12 weeks involving DPP-4 inhibitors was conducted.262 Of participants evaluated for the primary endpoint, 10,467 were treated with a DPP-4 inhibitor and 8,634 treated with placebo or a comparator drug. DPP-4 inhibitors showed a statistically significant reduction in HbA1c compared to placebo and approximately 40% of participants achieved the HbA1c goal of < 7%, which was associated with weight...
neutrality and no greater hypoglycemia. Baseline HbA1c was the best predictor for achievement of HbA1C target (p<0.001).

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

SUMMARY

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

The dipeptidyl peptidase-4 (DPP-4) inhibitors, indicated for adult patients with type 2 diabetes (T2DM), have modest glucose-lowering effects with HbA1c decrements of 0.5% to 1.0%. These agents are weight-neutral and have a low hypoglycemia risk when used as monotherapy or in conjunction with metformin. A once daily fixed-dose combination of a DPP-4 inhibitor and a sodium-dependent glucose cotransporter 2 (SGLT2) inhibitor, linagliptin/empagliflozin (Glyxambi), is also available and is associated with a reduction in body weight compared to linagliptin alone. Concerns regarding the increased risk of pancreatitis and pancreatic cancer remain unresolved, although recent data have indicated a lack of an association between DPP-4 inhibitors and pancreatic adverse effects. DPP-4 inhibitors are administered orally and are dosed once daily, except those that are available in combination with immediate-release metformin (alogliptin/metformin [Kazano], linagliptin/metformin [Jentadueto], and sitagliptin/metformin [Janumet]).

The glucagon-like peptide-1 (GLP-1) receptor agonists, albiglutide (Tanzeum), dulaglutide (Trulicity), exenatide (Byetta, Bydureon), liraglutide (Victoza), and lixisenatide (Adlyxin) are indicated for patients with T2DM. Based on clinical trials, administration of albiglutide is associated with an HbA1c reduction of 0.7% to 0.9%, dulaglutide with a reduction of 0.7% to 1.6%, exenatide and liraglutide with a reduction in HbA1c of 0.5% to 1.6%, and lixisenatide with a reduction of 0.3% to 0.65%. Many study participants experienced a decrease in weight of 0.4 kg to 3.5 kg from baseline. Risks of GLP-1 agonists include the potential for acute pancreatitis and thyroid C-cell tumors including medullary thyroid carcinoma. Hypoglycemia is not usually associated with GLP-1 agonist therapy, unless used in combination with an insulin secretagogue or insulin. GLP-1 agonists are administered by subcutaneous injection; exenatide (Byetta) is dosed twice daily, liraglutide and lixisenatide are dosed once daily, while long-acting albiglutide, dulaglutide, and exenatide ER (Bydureon) are dosed once weekly. Combination products offer an additional mechanism to lower blood glucose for patients not meeting HbA1c goals on monotherapy. Liraglutide/insulin degludec (Xultophy) and lixisenatide/insulin glargine (Soliqua) are fixed-dose combinations of a GLP-1 agonist and a long-acting insulin; both products are dosed once-daily.

Use of GLP-1 agonists have not been studied in patients with severe gastrointestinal disease, including severe gastroparesis; therefore, they are not recommended for patients with severe gastrointestinal disease.
As reported by the LEADER trial, liraglutide is associated with a significant 13% relative reduction (RR) in composite cardiovascular (CV) risk (death from CV cause, nonfatal myocardial infarction [MI], or nonfatal stroke). While the rate of death from CV or other causes was lower with liraglutide, the rates of nonfatal MI, nonfatal stroke, and hospitalization for heart failure were not statistically significantly lower than with placebo. The ELIXA study reported that lixisenatide (Adlyxin) has a neutral effect on CV risk.

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

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

REFERENCES

1 Symlin [package insert]. Wilmington, DE; AstraZeneca; February 2015.
2 Nesina [package insert]. Deerfield, IL; Takeda; December 2016.
3 Kazano [package insert]. Deerfield, IL; Takeda; December 2016.
4 Oseni [package insert]. Deerfield, IL; Takeda; December 2016.
5 Tradjenta [package insert]. Ridgefield, CT; Boehringer Ingelheim; December 2016.
6 Glyxambi [package insert]. Ridgefield, CT; Boehringer Ingelheim; December 2016.
7 Jentadueto [package insert]. Ridgefield, CT, Boehringer Ingelheim; December 2016.
8 Jentadueto XR [package insert]. Ridgefield, CT, Boehringer Ingelheim; December 2016.
14 Tanzeum [package insert]. Wilmington, DE; GlaxoSmithKline; September 2016.
16 Byetta [package insert]. Wilmington, DE; AstraZeneca; February 2015.
17 Byduereon [package insert]. Wilmington, DE; AstraZeneca; September 2015.
27 Symlin [package insert]. Wilmington, DE; AstraZeneca; February 2015.
28 Glyxambi [package insert]. Ridgefield, CT; Boehringer Ingelheim; December 2016.


36 Symlin [package insert]. Wilmington, DE; AstraZeneca; February 2015.


38 Kombiglyze XR [package insert]. Wilmington DE; AstraZeneca; February 2017.


41 Tradjenta [package insert]. Ridgefield, CT; Boehringer Ingelheim; December 2016.

42 Glyxambi [package insert]. Ridgefield, CT; Boehringer Ingelheim; December 2016.


47 Tanzeum [package insert]. Wilmington, DE; GlaxoSmithKline; September 2016.

48 Nesina [package insert]. Deerfield, IL; Takeda; December 2016.


50 Byetta [package insert]. Wilmington, DE; AstraZeneca; February 2015.

51 Bydureon [package insert]. Wilmington, DE; AstraZeneca; September 2015.

52 Gupta V. Glucagon-like peptide-1 analogues: An overview.


58 Nesina [package insert]. Deerfield, IL; Takeda; December 2016.

59 Kazano [package insert]. Deerfield, IL; Takeda; December 2016.

60 Oseni [package insert]. Deerfield, IL; Takeda; December 2016.

61 Byetta [package insert]. Wilmington, DE; AstraZeneca; February 2015.

62 Bydureon [package insert]. Wilmington, DE; AstraZeneca; September 2015.


64 Symlin [package insert]. Wilmington, DE; AstraZeneca; February 2015.


69 Kombiglyze XR [package insert]. Wilmington DE; AstraZeneca; February 2017.

70 Tradjenta [package insert]. Ridgefield, CT; Boehringer Ingelheim; December 2016.

71 Lentaduoeto [package insert]. Ridgefield, CT; Boehringer Ingelheim; December 2016.

72 Tanzeum [package insert]. Wilmington, DE; GlaxoSmithKline; September 2016.

73 Trulicity [package insert]. Indianapolis, IN; Eli Lilly; January 2017.

74 Glyxambi [package insert]. Ridgefield, CT; Boehringer Ingelheim; December 2016.


100. Kazano [package insert]. Deerfield, IL; Takeda; December 2016.
112. Tradjenta [package insert]. Ridgefield, CT; Boehringer Ingelheim; December 2016.
114. Glyxambi [package insert]. Ridgefield, CT; Boehringer Ingelheim; December 2016.
118. Symlin [package insert]. Wilmington, DE; AstraZeneca; February 2015.
120. Kazano [package insert]. Deerfield, IL; Takeda; December 2016.
121. Oseni [package insert]. Deerfield, IL; Takeda; December 2016.
122. Tradjenta [package insert]. Ridgefield, CT; Boehringer Ingelheim; December 2016.
123. Glyxambi [package insert]. Ridgefield, CT; Boehringer Ingelheim; December 2016.
125. Jentadueto XR [package insert]. Ridgefield, CT; Boehringer Ingelheim; December 2016.
141. Oseni [package insert]. Deerfield, IL; Takeda; December 2016.
143. Bydureon [package insert]. Wilmington, DE; AstraZeneca; September 2015.
144. Symlin [package insert]. Wilmington, DE; AstraZeneca; February 2015.
149 Kombiglyze XR [package insert]; Wilmington DE; AstraZeneca; February 2017.
150 Tradjenta [package insert]. Ridgefield, CT; Boehringer Ingelheim; December 2016.
151 Jentadueto [package insert]. Ridgefield, CT; Boehringer Ingelheim; December 2016.
152 Tanzeum [package insert]. Wilmington, DE; GlaxoSmithKline; September 2016.
154 Glyxambi [package insert]. Ridgefield, CT; Boehringer Ingelheim; December 2016.
158 Synmilar [package insert]. Wilmington, DE; AstraZeneca; February 2015.
159 Nesina [package insert]. Deerfield, IL; Takeda; December 2016.
160 Kazano [package insert]. Deerfield, IL; Takeda; December 2016.
161 Oseni [package insert]. Deerfield, IL; Takeda; December 2016.
162 Tradjenta [package insert]. Ridgefield, CT; Boehringer Ingelheim; December 2016.
163 Glyxambi [package insert]. Ridgefield, CT; Boehringer Ingelheim; December 2016.
164 Jentadueto [package insert]. Ridgefield, CT; Boehringer Ingelheim; July 2014.
165 Jentadueto XR [package insert]. Ridgefield, CT; Boehringer Ingelheim; December 2016.
166 Onglyza [package insert]. Princeton, NJ; Bristol-Myers Squibb; August 2015.
167 Kombiglyze XR [package insert]; Wilmington DE; AstraZeneca; February 2017.
171 Tanzeum [package insert]. Wilmington, DE; GlaxoSmithKline; September 2016.
173 Byetta [package insert]. Wilmington, DE; AstraZeneca; February 2015.
174 Bydureon [package insert]. Wilmington, DE; AstraZeneca; September 2015.
185 Oseni [package insert]. Deerfield, IL; Takeda; December 2016.
187 Kazano [package insert]. Deerfield, IL; Takeda; December 2016.
188 Kazano [package insert]. Deerfield, IL; Takeda; December 2016.
189 Kazano [package insert]. Deerfield, IL; Takeda; December 2016.
190 Oseni [package insert]. Deerfield, IL; Takeda; December 2016.
191 Oseni [package insert]. Deerfield, IL; Takeda; December 2016.
197 Glyxambi [package insert]. Ridgefield, CT; Boehringer Ingelheim; December 2016.
198 Jentadueto [package insert]. Ridgefield, CT, Boehringer Ingelheim; December 2016.
199 Jentadueto [package insert]. Ridgefield, CT, Boehringer Ingelheim; December 2016.
200 Jentadueto [package insert]. Ridgefield, CT, Boehringer Ingelheim; December 2016.
201 Jentadueto XR [package insert]. Ridgefield, CT, Boehringer Ingelheim; December 2016.
207 Onglyza [package insert]. Princeton, NJ; Bristol-Myers Squibb; August 2015.
208 Onglyza [package insert]. Princeton, NJ; Bristol-Myers Squibb; August 2015.
228 Trulicity [package insert]. Indianapolis, IN; Eli Lilly; January 2017.
236 Bydureon [package insert]. Wilmington, DE; AstraZeneca; September 2015.
244 Marre M, Shaw J, Brandle M, et al. LEAD-1 SU study group. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU). Diabet Med. 2009; 26(3): 268-278.