

Hypoglycemics, Incretin Enhancers/Mimetics Review

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Hypoglycemics, Incretin Enhancers/Mimetics Review

FDA-Approved Indications

Drug	Manufacturer	Indications
exenatide (Byetta™) ¹	Amylin/Lilly	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
liraglutide (Victoza®) ²	Novo Nordisk	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
pramlintide (Symlin®) ³	Amylin	Adjunct therapy in type 1 and type 2 diabetes patients who use mealtime insulin therapy and have failed to achieve desired glucose control despite optimal insulin therapy (with or without concurrent sulfonylurea and/or metformin in type 2 patients)
saxagliptin (Onglyza™) ⁴	Bristol-Myers Squibb	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
sitagliptin (Januvia™) ⁵	Merck	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes
sitagliptin/metformin (Janumet™) ⁶	Merck	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes when treatment with both agents is appropriate

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

Exenatide (Byetta), liraglutide (Victoza), and saxagliptin (Onglyza) have not been studied in combination with insulin.

Exenatide (Byetta), liraglutide (Victoza), sitagliptin (Januvia), and sitagliptin/metformin (Janumet) have not been studied in patients with a history of pancreatitis.

Overview

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

The products reviewed here are not listed as first-line options for the treatment of type 2

diabetes in the 2009 update to the American Diabetes Association (ADA) consensus algorithm.⁷ The consensus statement notes that the 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.

Although deemed a less well-validated regimen by the ADA, exenatide may be added if a patient has failed to meet glycemic goals with lifestyle modifications and metformin, and the avoidance of hypoglycemia and the promotion of weight loss are desirable. Candidates for the addition of exenatide should also have a hemoglobin A_{1c} (HbA_{1c}) of <8 percent. Liraglutide was not available at the time of publication.

The American Academy of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) 2009 recommendations for glycemic control in patients with type 2 diabetes includes DPP-4 inhibitor (sitagliptin or saxagliptin) as an initial treatment option, as well as most of the oral antidiabetic agents.⁸ For patients having inadequate treatment with monotherapy, DPP-4 inhibitors, and GLP-1 receptor agonists are recommended as options when initial pharmacologic therapy is not adequate.

Pharmacology⁹

Beta cells secrete amylin and insulin in response to food intake. Secretion patterns of amylin in fasting and postprandial situations are similar to insulin. In patients with type 1 or type 2 diabetes using insulin, beta cells do not secrete adequate amounts of insulin or amylin in response to food. While insulin aids in uptake of blood glucose by muscle, pramlintide (Symlin), a synthetic analog of amylin, affects the rate of glucose appearance by several mechanisms. Pramlintide slows gastric emptying, suppresses glucagon secretion, and centrally modulates appetite.

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

Incretins enhance glucose-dependent insulin secretion and exhibit other hypoglycemic actions following release into the circulation from the gut. Exenatide (Byetta) and liraglutide (Victoza), incretin mimetic and GLP-1 agonist agents, enhance glucose-dependent insulin secretion by the beta cell, suppress inappropriately elevated glucagon secretion, and slow gastric emptying. The amino acid sequence of exenatide partially overlaps that of human GLP-1. Liraglutide (Victoza) has 97 percent amino acid homology to endogenous human GLP-1. Exenatide promotes insulin release from beta cells in the presence of elevated glucose concentrations and restores first-phase insulin response.

Sitagliptin (Januvia) and saxagliptin (Onglyza) are DPP-4 enzyme inhibitors. Inhibiting the DPP-4 enzyme slows inactivation of GLP-1 and GIP, and prolongs the action of the incretins. DPP-4 inhibition increases insulin secretion and reduces glucagon secretion by preventing the inactivation of glucagon-like peptide-1 (GLP-1), thereby lowering glucose levels. Sitagliptin/metformin (Janumet) combines sitagliptin with metformin. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

Pharmacokinetics

Drug	Peak (hrs)	Half-life (hrs)	Metabolism	Excretion
exenatide (Byetta) ¹⁰	2.1	2.4	Predominantly by the kidneys	Predominantly by the kidneys
liraglutide (Victoza) ¹¹	8-12	13	Not specified	Excreted in urine and feces
pramlintide (Symlin) ¹²	0.33	0.8	Primarily by kidneys to des-lys pramlintide (active metabolite)	--
saxagliptin (Onglyza) ¹³	2	2.5	CYP3A4/5; active metabolite – 5-hydroxy saxagliptin which is one-half as potent as saxagliptin	Urine: 75% Feces: 22%
sitagliptin (Januvia) ¹⁴	1-4	12.4	Primarily by CYP3A4 (minor)	Urine: 87% Feces: 13%
sitagliptin / metformin (Janumet) ^{15,16}	1.4 4-7	12.4 6.2	Primarily by CYP3A4 (minor) None	Urine: 87% Feces: 13% Excreted unchanged in the urine

In bioequivalence studies, sitagliptin/metformin (Janumet) was bioequivalent to the single agents administered together.¹⁷

Contraindications/Warnings^{18,19,20,21,22}

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

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

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

Exenatide (Byetta), liraglutide (Victoza), and saxagliptin (Onglyza) have not been studied in combination with insulin.

Exenatide (Byetta), liraglutide (Victoza), sitagliptin (Januvia), and sitagliptin/metformin (Janumet) have not been studied in patients with a history of pancreatitis.

exenatide (Byetta)

Exenatide use has been associated with postmarketing reports of acute pancreatitis including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. After initiation of exenatide, and after dose increases, patients should be observed for signs and symptoms of pancreatitis including persistent severe abdominal pain, sometimes radiating to the back which may be accompanied by vomiting. If pancreatitis is suspected, discontinue exenatide promptly. If pancreatitis is confirmed, exenatide should not be restarted. Consider antidiabetic therapies other than exenatide in patients with a history of pancreatitis.

Exenatide should not be used in patients with severe renal impairment (CrCl < 30 mL/min) or end stage renal disease. Use exenatide with caution in patients with renal transplantation. In patients with moderate renal impairment (CrCl 30-50 mL/min), use caution when escalating exenatide dose from 5 to 10 mcg.

In post marketing reports, patients receiving exenatide have experienced altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure and acute renal failure sometimes requiring hemodialysis or kidney transplantation. Some of the events occurred in patients receiving one or more medications known to affect renal function or hydration status such as angiotensin converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), or diuretics. Some events occurred in patients who had been experiencing nausea, vomiting, or diarrhea, with or without dehydration. Reversibility of altered renal function has been observed. Direct nephrotoxic effects of exenatide have not been observed in clinical trials.

Patients with severe gastrointestinal disease such as gastroparesis should not receive exenatide.

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

Exenatide is not a substitute for insulin in patients who require insulin. Do not use in patients with type 1 diabetes or for treatment of type 1 diabetic ketoacidosis.

liraglutide (Victoza)

Liraglutide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

pramlintide (Symlin)

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

saxagliptin (Onglyza)

The risk of hypoglycemia increases when saxagliptin is given in combination with other drugs that can cause hypoglycemia, such as insulin secretagogues (e.g. sulfonylureas). Decrease the dose of the insulin secretagogue if given in combination with saxagliptin in order to decrease the risk of hypoglycemia.

sitagliptin/metformin (Janumet)

Sitagliptin/metformin carries boxed warning for lactic acidosis due to the accumulation of the metformin component. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure. Symptoms include malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. If acidosis is suspected, discontinue sitagliptin/metformin and hospitalize the patient immediately. Metformin is contraindicated in patients with a serum creatinine greater than or equal to 1.5 mg/dL (males) or greater than or equal to 1.4 mg/dL (females).

sitagliptin (Januvia) and sitagliptin/metformin (Janumet)

Sitagliptin has been associated with serious hypersensitivity reactions in post-marketing reports of patients treated with this medication. Reported reactions have varied in severity and include anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, exfoliative skin conditions such as Stevens-Johnson syndrome, elevations in hepatic enzymes, and pancreatitis. Onset of these reactions has occurred after the initial dose to within the first three months after starting treatment. Sitagliptin or sitagliptin/metformin should be discontinued immediately and alternative antidiabetic therapy initiated if a hypersensitivity reaction is suspected. Assess the patient for other potential causes of the suspected reaction and institute appropriate treatment and monitoring accordingly.

Postmarketing reports of acute pancreatitis including fatal and non-fatal hemorrhagic or necrotizing pancreatitis have been reported in patients on sitagliptin. Patients should be monitored carefully for signs and symptoms of pancreatitis after the initiation of therapy with sitagliptin. If pancreatitis is suspected, sitagliptin should be discontinued. It is unknown if patients with a history of pancreatitis are at an increased risk for development of pancreatitis associated with sitagliptin use.

Patients with moderate to severe renal insufficiency including ESRD requiring hemodialysis or peritoneal dialysis require a dosage adjustment for sitagliptin.

The risk of hypoglycemia increases when sitagliptin is given in combination with other drugs that can cause hypoglycemia, such as insulin secretagogues (e.g. sulfonylureas) or insulin. Decrease the dose of the insulin secretagogue or insulin if given in combination with sitagliptin (with or without metformin) in order to decrease the risk of hypoglycemia.

Precautions^{23,24,25,26,27}

exenatide (Byetta)

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. When used in combination with an insulin secretagogue, patients may be at increased risk for hypoglycemic episodes.

pramlintide (Symlin)

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

sitagliptin/metformin (Janumet)

Patients should be advised to avoid excessive alcohol intake. Sitagliptin/metformin should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function.

Drug Interactions^{28,29,30,31,32,33}

When used in combination with metformin, no increase in the incidence of hypoglycemia was observed with exenatide (Byetta) compared to placebo. However, use of exenatide with a sulfonylurea did increase the incidence of hypoglycemia. A reduced dose of sulfonylurea should be considered. Reports of elevation of INR in patients receiving both warfarin and exenatide have been published; monitoring of INR should be performed when exenatide therapy is initiated or altered.

The effect of exenatide and liraglutide on gastric emptying time may reduce the extent and rate of absorption of orally administered drugs. Patients should take oral medications at least one hour before exenatide injection. Liraglutide did not affect the absorption of tested orally administered medications to any clinically relevant degree; however, caution should be exercised when oral medications are given concomitantly with liraglutide.

When rapid onset of an oral medication is critical, drug should be administered at least one hour before or two hours after pramlintide (Symlin) due to effects on GI motility.

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

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

sitagliptin/metformin

Cationic drugs (e.g., amiloride, cimetidine, morphine, procainamide, quinidine, or triamterene) have the potential for interaction with metformin by competing for common renal transport systems. Such an interaction between metformin and oral cimetidine has been observed in normal healthy volunteers with a 60 percent increase in peak metformin plasma and whole blood concentrations. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and/or dose adjustment of sitagliptin/metformin and/or the interfering drug is recommended in patients who are taking cationic medications.

Adverse Effects

Drug	Nausea	Vomiting	Diarrhea	Headache	Hypoglycemia	URI
exenatide (Byetta) ³⁴	8-44 (0-18)	4-13 (0-4)	≥1-13 (0-6)	9 (6)	4.5-35.7 (3.3-12.6)	nr
liraglutide (Victoza) ³⁵	28.4	10.9	17.1	9.1	3.7-29.6 (2.5-16.7)	9.5
pramlintide (Symlin) ³⁶	28-48 (12-17)	7-11 (4-7)	nr	5-13 (7)	4.7-16.8 (2.1-10.8)	nr
saxagliptin (Onglyza) ³⁷	nr	2.2-2.3 (1.3)	nr	6.5 (5.9)	4.0-5.6 (4.1)	7.7 (7.6)
sitagliptin (Januvia) ³⁸	1.4 (0.6)	nr	3 (2.3)	1.1-5.9 (2.8-4.6)	0.6-15.5 (0.6-1.8)	4.5-6.3 (3.4-5.1)
sitagliptin/ metformin (Janumet) ³⁹	4.8 (1.1)	2.2 (0.6)	7.5 (4.0)	3.8 (2.8)	15.3-16.4 (0.9-8.2)	6.2 (5.1)

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

Peripheral edema was reported more commonly in patients treated with combination of saxagliptin and a thiazolidinedione; hypoglycemia was reported more commonly in patients treated with combination of saxagliptin and sulfonylurea. Hypersensitivity-related events, such as urticaria and facial edema in the five-study pooled analysis up to Week 24 were reported in 1.5 percent, 1.5 percent, and 0.4 percent of patients who received saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo, respectively.

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

Special Populations^{40,41,42,43,44,45}Pediatrics

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

Pregnancy

Sitagliptin (Januvia), sitagliptin/metformin (Janumet) and saxagliptin (Onglyza) are Pregnancy Category B. Exenatide (Byetta), liraglutide (Victoza), and pramlintide (Symlin) are Pregnancy Category C.

Renal Insufficiency

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

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

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

Hepatic Insufficiency

No dosage adjustment of saxagliptin (Onglyza) is recommended for patients with hepatic impairment. No dosage adjustment of sitagliptin is needed for patients with mild to moderate hepatic insufficiency. There is no clinical experience with sitagliptin in patients with severe hepatic insufficiency.

Sitagliptin/metformin use should be avoided in patients with hepatic disease.

Dosages

Drug	Dosing	Time of administration related to mealtime	Availability
exenatide (Byetta) ⁴⁶	5 mcg SC twice daily; dose can be increased to 10 mcg twice daily after one month	Administer at any time within the 60-minute period before the morning and evening meals preferably at least 6 hours apart	1.2, 2.4 mL prefilled pen containing 250 mcg/mL solution
liraglutide (Victoza) ⁴⁷	0.6 mg once daily subcutaneous injection into the upper arm, thigh or abdomen for one week. Dose may be increased to 1.2 mg once daily SC injection. Maximum dose is 1.8 mg daily.	Administer once daily at any time of day independent of meals. Injection site and timing can be changed without dose adjustment.	prefilled multidose pens that deliver 0.6 mg, 1.2 mg, and 1.8 mg doses. Pens contain 6 mg/mL (3 mL)
pramlintide (Symlin) ⁴⁸	type 1 diabetes: initiate at 15 mcg, titrate to 30 or 60 mcg by 15 mcg increments	Prior to major meals, concurrently with insulin; decrease insulin doses 50 percent initially, then adjust only after reaching the target dose of pramlintide	5 mL vial (0.6 mg/mL); 1.5, 2.7 mL pens (1 mg/mL)
	type 2 diabetes: initiate at 60 mcg, titrate to 120 mcg as tolerated		
saxagliptin (Onglyza) ⁴⁹	2.5 to 5 mg daily	Take with or without food	2.5, 5 mg tablets
sitagliptin (Januvia) ⁵⁰	100 mg once daily	Take with or without food	25, 50, 100 mg tablets
sitagliptin/metformin (Janumet) ⁵¹	one tablet twice daily	Take with food	50 mg/500 mg, 50 mg/1,000 mg tablets

For saxagliptin (Onglyza), patients with moderate to severe renal impairment (CrCl ≤ 50 ml/min), end-stage renal disease, and taking strong CYP3A4/5 inhibitors (ketoconazole, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin) should receive no more than 2.5 mg once daily.⁵²

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

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

Doses of exenatide (Byetta) or insulin should be injected in the thigh, abdomen, or upper arm, rotating sites regularly.

Clinical Trials

Search Strategies

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

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

exenatide (Byetta)

A triple-blind, placebo-controlled, multicenter, 30-week study evaluated exenatide in patients with type 2 diabetes who had inadequate treatment with sulfonylureas.⁵³ After a four-week, single-blind, placebo lead-in period, 377 subjects were randomized and began four weeks of 5 mcg subcutaneous exenatide or placebo twice daily. The dose of exenatide in the active treatment arm increased to 10 mcg twice daily after four weeks. All subjects continued sulfonylurea therapy. At week 30, HbA_{1c} changes from baseline were -0.86, -0.46, and +0.12 percent in the exenatide 10 mcg, 5 mcg, and placebo arms, respectively (adjusted p<0.001). Of evaluable subjects with baseline HbA_{1c} > 7 percent (n=237), 41 percent (exenatide 10 mcg), 33 percent (exenatide 5 mcg), and 9 percent (placebo) achieved HbA_{1c} ≤ 7 percent (p<0.001). Patients in the exenatide arms had dose-dependent progressive weight loss, with an end-of-study loss in the 10 mcg exenatide arm of -1.6 kg from baseline (p<0.05 versus placebo). Adverse events were generally mild or moderate and primarily gastrointestinal. Another study of 336 patients found similar results when using exenatide in combination with metformin alone.⁵⁴ Some authors credited with the publications have been involved with manufacturer-funded studies of exenatide.

A double-blind, placebo-controlled study with 733 patients with type 2 diabetes found comparable results at 30 weeks using the same treatment arms as the above study, with the addition of metformin to a sulfonylurea.⁵⁵ At week 30, HbA_{1c} 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 percent for exenatide 10 mcg and -0.8 percent for exenatide 5 mcg groups. In the evaluable population, exenatide-treated patients were more likely to achieve HbA_{1c} ≤ 7 percent than placebo-treated patients (34 percent, exenatide 10 mcg group; 27 percent, exenatide 5 mcg group; and nine percent, placebo; p<0.0001). Weight loss occurred in both exenatide treated groups (-1.6 kg, p≤0.01 versus placebo). Mild or moderate

nausea was the most frequently reported adverse event. Hypoglycemia was reported in 28 percent of exenatide 10 mcg group, 19 percent of exenatide 5 mcg group, and 13 percent of the placebo group.

exenatide (Byetta) and insulin glargine (Lantus®)

In a 26-week multicenter, open-label, randomized, controlled trial, 551 patients with type 2 diabetes and inadequate glycemic control despite combination metformin and sulfonylurea therapy were randomized to treatment with exenatide 10 mcg twice daily or insulin glargine once daily.⁵⁶ At week 26, both exenatide and insulin glargine reduced HbA_{1c} levels by 1.11 percent. Insulin glargine reduced fasting glucose concentrations more than exenatide. Body weight decreased 2.3 kg with exenatide and increased 1.8 kg with insulin glargine. Rates of symptomatic hypoglycemia were similar, but nocturnal hypoglycemia occurred less frequently with exenatide (0.9 events/patient-year versus 2.4 events/patient-year). Nausea (57.1 versus 8.6 percent), vomiting (17.4 versus 3.7 percent), and diarrhea (8.5 versus three percent) were more common in the exenatide group than in the insulin glargine group.

A randomized, open-label, crossover, noninferiority study compared the efficacy of exenatide 10 mcg twice daily and insulin glargine once daily for 16 weeks in patients (n=138) with type 2 diabetes inadequately treated with metformin or a sulfonylurea.⁵⁷ The primary outcome variable was the change in HbA_{1c}. Secondary outcomes included the proportion of patients achieving HbA_{1c} of ≤ 7 percent, the change in fasting plasma glucose (FPG), and change in body weight. Both exenatide and insulin glargine were associated with similar significant changes from baseline (mean HbA_{1c} 8.95 percent) in HbA_{1c} (both -1.36 percent; $p < 0.001$ versus baseline). Similar proportions of patients achieved HbA_{1c} ≤ 7 percent (37.5 and 39.8 percent, respectively; $p = \text{NS}$). Patients lost weight during exenatide treatment, whereas they gained weight during insulin glargine treatment; (mean difference, -2.2 kg; $p < 0.001$). Both exenatide and insulin glargine were associated with significant reductions from baseline in FPG, although the reduction was significantly greater with insulin glargine compared with exenatide (mean difference, 1.2 mmol/L; $p < 0.001$). The percentages of patients reporting nausea during exenatide and insulin glargine treatment were 42.6 and 3.1 percent, respectively; the incidence of hypoglycemia was 14.7 and 25.2 percent, respectively ($p = \text{NS}$).

liraglutide (Victoza)

Liraglutide was evaluated in the Liraglutide Effect and Action in Diabetes (LEAD) trials, in 3,978 adults with type 2 diabetes in five double-blind (one of these used an open-label active control insulin glargine arm), randomized, controlled, multicenter clinical trials.⁵⁸ In each of these trials, treatment with liraglutide produced clinically and statistically significant improvements in HbA_{1c} and fasting plasma glucose (FPG). Liraglutide was initiated at a dose of 0.6 mg/day. The dose was increased by 0.6 mg weekly increments to reach 1.2 mg or 1.8 mg final doses. In the LEAD studies, liraglutide did not have adverse effects on blood pressure.

LEAD-3 Mono was a 52-week trial with 746 patients randomized to liraglutide 1.2 mg or 1.8 mg or glimepiride 8 mg.⁵⁹ The primary outcome was change in HbA_{1c}. HbA_{1c} decreased by 0.51 percent with glimepiride versus 0.84 percent with liraglutide 1.2 mg (difference -0.33%; 95% CI, -0.53 to -0.13, $p < 0.05$) and 1.14 percent with liraglutide 1.8 mg (difference -0.62%; 95% CI, -0.83 to -0.42, $p < 0.0001$). Five patients discontinued therapy due to vomiting in the liraglutide 1.2 mg group, one patient in 1.8 mg group, and zero patients in the glimepiride group. Discontinuations due to ineffective therapy were 3.6 percent in the liraglutide 1.8 mg group, 6 percent in the liraglutide 1.2 mg group, and 10.1 percent in the glimepiride group. Liraglutide

1.8 and 1.2 mg resulted in 2.5 and 2.1 kg weight loss ($p < 0.0001$) compared to a 1.1 kg weight gain with glimepiride.

Add-on to Metformin: This was a 26-week trial of 1,091 patients randomized to liraglutide 0.6 mg, 1.2 mg, 1.8 mg, placebo or glimepiride 4 mg, all as add-on to metformin 2,000 mg.⁶⁰ HbA_{1c} increased by 0.1 percent with placebo/metformin, decreased by 1 percent with glimepiride/metformin, decreased by 1 percent in both liraglutide 1.2 mg and 1.8 mg groups ($p < 0.0001$ for the liraglutide groups). Discontinuations due to ineffective therapy were 5.4 percent in the liraglutide 1.8 mg/metformin group, 3.3 percent in the liraglutide 1.2 mg/metformin group, 23.8 percent in the placebo/metformin group, and 3.7 percent in the glimepiride/metformin group. The liraglutide 1.8 mg/metformin and liraglutide 1.2 mg/metformin groups had a weight loss of 2.8 and 2.6 kg, respectively ($p < 0.05$) compared to a 1.5 kg decrease in the placebo/metformin and 1 kg increase in the glimepiride/metformin groups.

LEAD-1 SU: This was a 26-week 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).⁶¹ Liraglutide 1.2 or 1.8 mg resulted in greater reductions in HbA_{1c} (-1.1 percent each, $p < 0.0001$), compared with placebo (+0.2 percent, $p < 0.0001$) or rosiglitazone (-0.4 percent, $p < 0.0001$) when added to glimepiride. Changes in body weight seen were: liraglutide 1.8 mg (-0.2 kg), liraglutide 1.2 mg (+0.3 kg), placebo (-0.1 kg), and rosiglitazone (+2.1 kg, $p < 0.0001$). Main adverse events for all treatments were minor hypoglycemia (<10 percent), nausea (<11 percent), vomiting (<5 percent) and diarrhea (<8 percent). The percentage of patients who discontinued due to ineffective therapy was 3 percent in the liraglutide 1.8 mg/glimepiride group, 3.5 percent in the liraglutide 1.2 mg/glimepiride group, 17.5 percent in the placebo/glimepiride group, and 6.9 percent in the rosiglitazone/glimepiride group.

LEAD-5 met+SU: This was a 26-week study of 581 patients randomized to liraglutide 1.8 mg, placebo, or insulin glargine open-label arm (dose could be adjusted), all as add-on to metformin 2,000 mg or glimepiride 4 mg.⁶² The liraglutide group resulted in 1.3 percent decrease ($p < 0.0001$) in HbA_{1c} compared to 0.2 percent decrease with placebo, and 1.1 percent decrease in the insulin group. The difference in HbA_{1c} 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 1.4 kg in the insulin group. Rates of hypoglycemic episodes (major, minor and symptoms only, respectively) were 0.06, 1.2, and 1 events/patient/year, respectively, in the liraglutide group (compared with 0, 1.3, 1.8 events/patient/year and 0, 1, 0.5 events/patient/year with insulin and placebo, respectively). A higher number of adverse events, including 14 percent nausea, were reported with liraglutide. Discontinuation percentages due to ineffective therapy were 0.9 percent in the liraglutide 1.8 mg group, 0.4 percent in the insulin glargine group, and 11.3 percent in the placebo group.

LEAD-4 met+TZD: This was a 26-week 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. HbA_{1c} significantly decreased by 1.5 percent in each of the liraglutide groups compared to a 0.5 percent decrease in the placebo group.⁶³ Dose-dependent weight loss occurred with liraglutide 1.2 and 1.8 mg groups, 1 kg and 2 kg, respectively ($p < 0.0001$) compared with weight gain with placebo (0.6 kg). Minor hypoglycemia was reported more frequently with liraglutide, but no major hypoglycemia occurred. Gastrointestinal adverse events were more common with liraglutide; however, most GI events occurred early in therapy and were transient. Discontinuation percentages due to ineffective therapy were 1.7 percent in the liraglutide 1.8 mg group, 1.7 percent in the liraglutide 1.2 mg group, and 16.4 percent in the placebo group.

pramlintide (Symlin)

In a double-blind, placebo-controlled, parallel-group, multicenter study, 651 patients with type 1 diabetes were randomized to mealtime injections of placebo or pramlintide in addition to insulin therapy for 52 weeks.⁶⁴ Addition of pramlintide 60 mcg three or four times daily to insulin resulted in significant reductions in HbA_{1c} from baseline of 0.29 percent ($p < 0.011$) and 0.34 percent ($p < 0.001$), respectively, compared to a 0.04 percent reduction in the placebo group at 52 weeks. Greater reduction in HbA_{1c} with pramlintide was achieved without an increase in concomitant insulin use and was accompanied by a significant reduction in body weight from baseline to week 52 of -0.4 kg in the pramlintide 60 mcg three ($p < 0.027$) or four times daily ($p < 0.04$) groups. The placebo group had a +0.8 kg weight gain. The most frequent adverse event in pramlintide-treated patients was nausea.

A 29-week, double-blind, placebo-controlled study randomized 296 patients with type 1 diabetes to pramlintide or placebo as an adjunct to insulin.⁶⁵ Insulin use was adjusted as needed. Baseline HbA_{1c} was 8.1 percent for both groups. At week 29, HbA_{1c} reductions were similar for both study arms (both -0.5 percent). Pramlintide treatment significantly reduced postprandial glucose excursions ($p < 0.0005$) and weight (pramlintide -1.3 ± 0.30 kg; placebo $+1.2 \pm 0.30$ kg; $p < 0.0001$). At week 29, insulin dose decreased by 28 and 4 percent in pramlintide- and placebo-treated groups, respectively. Nausea was reported by 63 and 36 percent of patients in pramlintide and placebo groups ($p < 0.01$), respectively, and severe hypoglycemia rates were 0.57 for pramlintide and 0.30 for placebo (event rate/patient-year; $p < 0.05$).

In a 52-week, double-blind, placebo-controlled, parallel-group, multicenter study, 656 patients with type 2 diabetes treated with insulin alone or in combination with sulfonylureas and/or metformin were randomized to receive additional preprandial injections of either placebo or pramlintide.⁶⁶ 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 HbA_{1c} from baseline (-0.68 and -0.62 percent at weeks 26 and 52, respectively), compared to placebo ($p < 0.05$). The percentage of patients achieving HbA_{1c} < 8 percent was 46 percent for the pramlintide group and 28 percent for the placebo group ($p < 0.05$). Glycemic improvement with pramlintide 120 mcg twice daily was accompanied by a mean weight loss of -1.4 kg compared to weight gain of +0.7 kg with placebo at week 52 ($p < 0.05$). The most common adverse event associated with pramlintide use was transient, mild to moderate nausea.

saxagliptin (Onglyza)

The efficacy and safety of once-daily saxagliptin monotherapy was evaluated in treatment-naïve patients with type 2 diabetes and inadequate glycemic control for 24 weeks.⁶⁷ The study enrolled 401 patients with HbA_{1c} of seven to 10 percent. These patients were randomized and treated with oral saxagliptin 2.5, 5, or 10 mg once daily or placebo. Primary endpoint was HbA_{1c} change from baseline to week 24, and secondary endpoints included change from baseline to week 24 in fasting plasma glucose (FPG), proportion of patients achieving HbA_{1c} < 7 percent, and changes in postprandial glucose area-under-the-curve (PPG-AUC). Results demonstrated that saxagliptin significantly decreased HbA_{1c} by -0.43 percent, -0.46 percent, -0.54 percent for saxagliptin 2.5, 5, and 10 mg, respectively, versus +0.19 percent for placebo ($p < 0.0001$, all values). Adjusted mean FPG was significantly reduced from baseline (-15, -9, and -17 mg/dL) for saxagliptin 2.5, 5, and 10 mg, respectively, versus +6 mg/dL for placebo ($p = 0.0002$, $p = 0.0074$, $p < 0.0001$, respectively). Goal attainment of HbA_{1c} of < 7 percent was achieved by week 24 in 35 percent ($p = \text{NS}$), 38 percent ($p = 0.0443$), 41 percent ($p = 0.0133$) for saxagliptin 2.5 mg, 5 mg, and 10 mg groups where as placebo rate was 24 percent. PPG-AUC was reduced for saxagliptin at all doses versus placebo with statistical significance

demonstrated for saxagliptin 5 mg ($p=0.0002$) and 10 mg ($p<0.0001$). Adverse event frequency was similar across all study arms. No cases of confirmed hypoglycemia (symptoms, with fingerstick glucose ≤ 50 mg/dL) were observed. Saxagliptin was not associated with weight gain.

A randomized, 24-week, Phase III, double-blind trial evaluated the efficacy and safety of saxagliptin added to a submaximal sulfonylurea dose in comparison to uptitration of sulfonylurea monotherapy in patients with type 2 diabetes taking sulfonylurea monotherapy with inadequate glycemic control.⁶⁸ Initially, all patients received open-label glyburide 7.5 mg daily for four weeks. A total of 768 patients between 18 to 77 years of age with HbA_{1c} screening value of 7.5 to 10 percent were randomized and treated with saxagliptin 2.5 or 5 mg in combination with glyburide 7.5 mg versus glyburide 10 mg monotherapy for 24 weeks. Blinded uptitration glyburide was allowed in the glyburide-only arm to a maximum total daily dose of 15 mg. Results indicated that at 24 weeks, 92 percent of glyburide-only patients were uptitrated to a total daily glyburide dose of 15 mg. Saxagliptin 2.5 and 5 mg provided statistically significant adjusted mean decreases from baseline to week 24 versus uptitrated glyburide in HbA_{1c} (-0.54 percent, -0.64 percent versus +0.08 percent, respectively; both $p<0.0001$) and fasting plasma glucose (-7, -10 versus +1 mg/dL, respectively; $p=0.0218$ and $p=0.002$). The proportion of patients achieving an HbA_{1c} <7 percent was greater for saxagliptin 2.5 and 5 mg versus uptitrated glyburide (22.4 percent and 22.8 percent versus 9.1 percent, respectively; both $p<0.0001$). Postprandial glucose area under the curve was reduced for saxagliptin 2.5 and 5 mg versus uptitrated glyburide (both $p<0.0001$). Adverse event occurrence was similar across all groups. Reported hypoglycemic events were not statistically significantly different for saxagliptin 2.5 and 5 mg versus uptitrated glyburide (13.3 percent and 14.6 percent versus 10.1 percent, respectively).

A multicenter, randomized, double-blind, active-controlled, Phase III trial evaluated the efficacy and safety of initial therapy with saxagliptin in combination with metformin versus saxagliptin monotherapy and metformin monotherapy in 1,306 treatment naïve patients with diabetes mellitus type 2.⁶⁹ Patients enrolled in the study were 18 to 77 years old, had HbA_{1c} 8 to 12 percent, fasting C-peptide concentration ≥ 1 ng/ml, and body mass index ≤ 40 kg/m². Patients were randomized to receive saxagliptin 5 mg or 10 mg with metformin 500 mg, saxagliptin 10 mg with placebo, or metformin 500 mg with placebo for 24 weeks. Metformin was titrated over the first five weeks to a maximum of 2,000 mg per day. The main outcome measure was change in HbA_{1c} from baseline to week 24, and secondary outcomes included change from baseline to week 24 in fasting plasma glucose (FPG), proportion of patients achieving HbA_{1c} <7 percent, and postprandial glucose area under the curve (PPG-AUC). Results indicated that at week 24, saxagliptin combination therapy with metformin demonstrated statistically significant adjusted mean decreases versus saxagliptin 10 mg and metformin monotherapies in HbA_{1c} (-2.5 and -2.5 percent versus -1.7 and -2.0 percent, all $p<0.0001$ versus monotherapy) and FPG (-60 and -62 mg/dL versus -31 and -47 mg/dL, both $p<0.0001$ versus saxagliptin 10 mg; $p=0.0002$ saxagliptin 5 mg + metformin versus metformin; $p<0.0001$ saxagliptin 10 mg + metformin versus metformin).. The proportion of patients achieving an HbA_{1c} <7 percent was greater with combination therapy versus monotherapy (all $p<0.0001$). PPG-AUC was significantly reduced for saxagliptin combination therapies versus saxagliptin 10 mg and metformin monotherapies (all $p<0.0001$ versus monotherapy). Adverse event occurrence was similar across all groups, and hypoglycemic events were infrequent.

A randomized, double-blind, placebo-controlled, 24-week trial evaluated the safety and efficacy of saxagliptin as add-on therapy to metformin versus placebo in patients with type 2 diabetes.⁷⁰ Seven-hundred forty-three patients with inadequate glycemic control on metformin monotherapy and HbA_{1c} ≥ 7 percent and ≤ 10 percent were randomly assigned to either saxagliptin at three different doses (2.5, 5, or 10 mg once daily) or placebo as an adjunct to a stable dose of

metformin (1,500-2,500 mg). Primary endpoint was HbA_{1c} change from baseline to week 24, and secondary endpoints included change from baseline to week 24 in fasting plasma glucose (FPG), percent of patients achieving HbA_{1c} <7 percent, and changes in postprandial glucose area-under-the-curve (PPG-AUC). Results demonstrated that saxagliptin 2.5, 5, and 10 mg plus metformin demonstrated statistically significant adjusted mean decreases from baseline to week 24 versus the control group in HbA_{1c} (all p<0.0001), FPG (all p<0.0001), and PPG-AUC (all p<0.0001). HbA_{1c} reductions for saxagliptin 2.5, 5, and 10 mg groups were -0.59, -0.69, and -0.58 percent versus placebo group reporting HbA_{1c} +0.13 percent. The percentages of patients achieving HbA_{1c} of <7 percent were 37, 44, and 44 percent for the saxagliptin 2.5, 5 and 10 mg groups compared to 17 percent for placebo (all p<0.0001). Incidence of hypoglycemic adverse events and weight reductions were similar between the two groups.

The efficacy and safety of saxagliptin plus TZD in 565 patients with type 2 diabetes and inadequate glycemic control on TZD monotherapy was evaluated in a multicenter, randomized, double-blind, Phase III study.⁷¹ Patients had a baseline HbA_{1c} of 7 - 10.5 percent while on pioglitazone 30 or 45 mg or rosiglitazone 4 or 8 mg for at least 12 weeks before screening.. Patients were given saxagliptin 2.5 or 5 mg once daily or placebo plus a stable TZD dose for 24 weeks. The adjusted mean decreases in HbA_{1c} versus placebo from baseline to week 24, the primary outcome parameter, was -0.66 percent (p=0.0007) for saxagliptin 2.5 mg and -0.94 percent (p<0.0001) for saxagliptin 5 mg compared to -0.3 percent with placebo. The percentage of patients achieving HbA_{1c} <7 percent was 42.2 (p=0.001), 41.8 (p=0.0013), and 25.6 percent for saxagliptin 2.5, 5 mg plus TZD, and placebo groups, respectively. Hypoglycemic events were similar across all groups.

sitagliptin (Januvia)

The efficacy and safety of sitagliptin was evaluated in a randomized, double-blind study with 701 patients with type 2 diabetes who were on metformin and evaluated for 24 weeks.⁷² Patients had a baseline HbA_{1c} of ≥7 percent to ≤10 percent (baseline of 8 percent) and on metformin 1,500 mg daily or more. Sitagliptin 100 mg daily or placebo were added. After 24 weeks, HbA_{1c} were reduced by -0.65 percent by sitagliptin. Significantly more patients on sitagliptin (47 percent) achieved HbA_{1c} of <7 percent compared to placebo (18.3 percent). Body weight decreased similarly in both groups. Sitagliptin was well tolerated. Another study of similar design with sitagliptin added to ongoing metformin therapy demonstrated similar reductions of HbA_{1c}.⁷³

sitagliptin (Januvia) and sitagliptin/metformin (Janumet)

In a 24-week, double-blind, placebo-controlled, parallel-group study, 1,091 patients with type 2 diabetes and HbA_{1c} 7.5 to 11 percent were randomized to sitagliptin 100 mg/metformin 1,000 mg, sitagliptin 100 mg/metformin 2,000 mg, metformin 1,000 mg, or metformin 2,000 mg in divided doses twice daily, sitagliptin 100 mg daily, or placebo.⁷⁴ Patients who had an HbA_{1c} >11 percent or a fasting glucose value >280 mg/dl after the run-in period were not eligible to be randomized. The mean baseline HbA_{1c} was 8.8 percent. The placebo-subtracted HbA_{1c} changes from baseline were -2.07 percent (sitagliptin/metformin 2,000 mg), -1.57 percent (sitagliptin/metformin 1,000 mg), -1.30 percent (metformin 2,000 mg), -0.99 percent (metformin 1,000 mg), and -0.83 percent (sitagliptin 100 mg) (p<0.001 for comparisons versus placebo and for coadministration versus respective monotherapies). The percentage of patients achieving HbA_{1c} <7 percent was 66 percent for sitagliptin/metformin 2,000 mg group (p<0.001 versus sitagliptin monotherapy and metformin 2,000 mg groups). The incidence of hypoglycemia was low (0.5 to 2.2 percent) across active treatment groups and not significantly different from that in the placebo group (0.6 percent).

sitagliptin (Januvia) and glipizide (Glucotrol®)

Patients (n=1,172) were randomized in a double-blind manner to the addition of sitagliptin 100 mg or glipizide 5 mg (maximum of 20 mg) daily to metformin for 52 weeks in a noninferiority trial.⁷⁵ From a mean baseline HbA_{1c} of 7.5 percent, changes from baseline were -0.67 percent at week 52 in both groups, confirming noninferiority. The proportions of patients achieving an HbA_{1c} <7 percent were 63 percent for sitagliptin and 59 percent for glipizide. The proportion of patients experiencing hypoglycemia was significantly higher with glipizide than with sitagliptin (32 versus 5 percent; p<0.001). Sitagliptin led to weight loss (-1.5 kg) compared with weight gain (+1.1 kg) with glipizide (p<0.001).

sitagliptin (Januvia) and TZDs

Patients (n=273) on metformin were randomized in a double-blind manner to receive the addition of sitagliptin 100 mg, rosiglitazone 8 mg, or placebo once daily for 18 weeks.⁷⁶ Change in HbA_{1c} from baseline was the primary endpoint. After 18 weeks, both active add-on therapies led to greater improvements in HbA_{1c} from the mean 7.7 percent baseline: -0.73 percent for sitagliptin (p<0.001 versus placebo) and -0.79 percent for rosiglitazone compared with -0.22 percent for placebo (p<0.001 versus placebo for both). No significant difference was observed between the sitagliptin and rosiglitazone treatments (0.06%, 95% CI, -0.14 to 0.25). The percentage of patients achieving HbA_{1c} <7 percent was 55 percent with sitagliptin and 63 percent with rosiglitazone and 38 percent for placebo. Body weight increased from baseline with rosiglitazone (1.5 kg) compared with a reduction in weight with sitagliptin (-0.4 kg) and placebo (-0.9 kg). The difference in body weight between the sitagliptin and rosiglitazone groups was 1.9 kg (95% CI, 1.3-2.5), and the proportion of patients experiencing a greater than 3 kg increase in body weight was 21 percent in the rosiglitazone group compared with two percent in both the sitagliptin and placebo groups. Both active treatments were generally well tolerated, with no increased risk of hypoglycemia or gastrointestinal adverse events compared with placebo.

The efficacy and tolerability of sitagliptin added to pioglitazone (Actos®) therapy were assessed in patients with type 2 diabetes and HbA_{1c} ≥7 percent and ≤10 percent while receiving a stable dose of pioglitazone of 30 to 45 mg per day.⁷⁷ In a multicenter, randomized, double-blind, placebo-controlled, parallel-group study, patients (n=353) were randomized to receive sitagliptin 100 mg daily or placebo for 24 weeks. The primary efficacy end point was change from baseline in HbA_{1c} at week 24. Mean baseline HbA_{1c} was 8.1 percent in the sitagliptin group and 8 percent in the placebo group. After 24 weeks, sitagliptin added to pioglitazone therapy was associated with significant reductions in HbA_{1c} (-0.70 percent; p<0.001) and fasting plasma glucose (FPG) (-17.7 mg/dL; p<0.001) compared with placebo. Mean HbA_{1c} values at study endpoint were 7.2 percent and 7.8 percent in the sitagliptin and placebo groups, respectively, and the proportions of patients reaching a target HbA_{1c} of <7 percent were 45.4 and 23 percent, respectively (p<0.001). Sitagliptin was generally well tolerated, with no increased risk of hypoglycemia compared with placebo.

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.⁷⁸ Studies were at least 12 weeks in duration and analyzed for HbA_{1c}, body weight changes, and hypoglycemia and other adverse events. A total of 5,429 patients with type 2 diabetes received either GLP-1 agonist with 3,053 patients received either placebo or an active comparator. A significant improvement in HbA_{1c} over placebo was observed (-1, 95% CI, -1.1 to -0.8; p<0.001). Low rates of

hypoglycemia were observed. Gastrointestinal adverse effects are reported frequently; however, weight loss is reported. No evidence of increased cardiovascular risk with the use of GLP-1 receptor agonists was found. GLP-1 receptor agonists result in both weight loss and gastrointestinal adverse effects. GLP-1 receptor agonists effectively reduce HbA_{1c} 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.

Summary

Exenatide (Byetta), liraglutide (Victoza), and pramlintide (Symlin) are adjunctive therapies for patients with diabetes. Administration of exenatide and liraglutide are typically associated with a reduction in HbA_{1c} of 0.5-1.1 percent, according to clinical trials. Many study participants experienced a decrease in weight of 1.5-2.0 kg from baseline, compared to weight gain in patients taking placebo. For pramlintide, HbA_{1c} improvements are 0.3-0.6 percent with potential weight reduction of 0.5-1.5 kg. This reduction comes with a greater risk of hypoglycemia and nausea.

Sitagliptin (Januvia) and saxagliptin (Onglyza) offer a novel mechanism of action and a modest decrease in HbA_{1c}. Comparisons with other oral antidiabetic drugs show that the effects of sitagliptin and saxagliptin on HbA_{1c} are comparable when used in combination with other agents. Comparative studies of DPP-4 inhibitors are currently lacking. Sitagliptin, saxagliptin, and sitagliptin/metformin (Janumet) are alternatives to the second-line agents, thiazolidinediones (TZDs), insulins, and sulfonylureas. Sitagliptin and saxagliptin are well tolerated with a low incidence of hypoglycemia.

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