Dipeptidyl Peptidase-4 (DPP-4) Inhibitors In the Management of Diabetes

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INTRODUCTION

Type-2 diabetes mellitus is a growing global public health concern. In the U.S., more than 23 million adults and children have diabetes (approximately 8% of the total population).[1] Diabetes is associated with many health complications, including cardiovascular disease, nephropathy, retinopathy, and neuropathy. In addition, the estimated cost to the health care system is more than $170 billion each year to treat these patients.[1]

Current oral treatment modalities for type-2 diabetes are aimed at suppressing hepatic glucose output, stimulating insulin release, mitigating glucose absorption, and increasing peripheral glucose utilization. Although these agents treat the resultant hyperglycemia associated with type-2 diabetes, the effects on the pathophysiological decline in beta-cell function and mass are not generally affected and the effects on beta-cell function have not been well studied over the long term. These agents—including biguanides (e.g., Glucophage), sulfonylureas (e.g., DiaBeta, Micronase, Glucotrol, Amaryl), meglitinides (e.g., Prandin, Novo Nordisk), alpha-glucosidase inhibitors (e.g., Glyset, Precose), and thiazolidinediones (e.g., Actos, Avandia)—are also often associated with significant adverse reactions.[2]

Starting in October 2006, sitagliptin (Januvia, Merck) was the first agent in the dipeptidyl peptidase-4 (DPP-4) inhibitor class to gain FDA approval in the U.S. This class of agents represents a novel target in the treatment of diabetes and may be combined with current modalities to improve glycemic control.

CLASSIFICATION AND PRODUCT INFORMATION

The DPP-4 inhibitors sitagliptin and saxagliptin (Onglyza, Bristol-Myers Squibb/AstraZeneca) belong to a class of antihyperglycemic agents indicated for improving glycemic control in patients with type-2 diabetes. Sitagliptin is available as 25-, 50-, and 100-mg tablets. A sitagliptin/metformin combination (Janumet, Merck) was approved in April 2007 in tablet strengths of 50 mg/500 mg and 50 mg/1,000 mg, respectively. Saxagliptin tablets, approved in July 2009, are sold in strengths of 2.5 and 5 mg. Both agents have been used as monotherapy and in combination with other antidiabetic drugs to help patients achieve blood glucose goals. Although these agents have modest efficacy, they represent an important class of compounds that provide another alternative or adjunct to metformin (Glucophage, Bristol-Myers Squibb) and other traditional therapies for type-2 diabetes.

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PHARMACOLOGY

Research into the role of gut hormones in the regulation of pancreatic beta-cell function has led to new targets in the management of type-2 diabetes. It is known that eating food leads to the release of multiple hormones that regulate gut motility, the secretion of gastric and pancreatic enzymes, the contraction of the gallbladder, and the absorption of various nutrients.[3] Several hormones facilitate the process of glucose removal by stimulating the release of insulin from the pancreas. The two main hormones involved in this endocrine signaling from the gut are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP).[3,4]

Secretion of GLP-1 occurs from the enteroendocrine L cells of the distal small intestine, whereas GIP is mainly secreted from the K cells in the proximal small intestine.[4] In the early 1900s, research involving the treatment of glycosuria with the administration of intestinal extracts first supported the incretin (INtestinal seCRETion of INsulin) effect that is mediated by these hormones.[5] The incretin effect refers to the greater amount of insulin secretion noted with giving oral glucose versus a comparable intravenous (IV) dosage, suggesting that oral ingestion stimulates pancreatic beta cells and the regulation of glucose.[2] This effect is reduced in patients with type-2 diabetes and is thought to be related to decreased insulinotropic action of GIP but not GLP-1.[4] In addition, continuous infusions of GLP-1 increase insulin secretion in patients with type-2 diabetes; however, higher doses of GIP have not been shown to do the same.[2] These attributes of GLP-1 make it an opportune target for the management of type-2 diabetes.

The role of GLP-1 in lowering blood glucose levels occurs via several mechanisms in addition to insulin secretion, including a reduction in glucagon concentrations, a delay of gastric emptying, and potential induction of satiety. GLP-1 may also play a role in the proliferation of beta cells and the decrease in beta-cell apoptosis.[2] Circulating levels of GLP-1 are low in the fasting state and rise quickly after meals; these circulating levels also decrease rapidly (half-life, less than 2 minutes) because of inactivation by the proteolytic enzyme, DPP-4. DPP-4 inhibitors, such as sitagliptin and saxagliptin, slow the inactivation and degradation of GLP-1, offering the newest FDA-approved treatment approaches for type-2 diabetes.[3]

PHARMACOKINETICS

Available DPP-4 inhibitors have been studied to determine parameters of absorption, distribution, metabolism, and excretion.

Absorption. A study of oral and IV administration of sitagliptin in healthy volunteers demonstrated 87% bioavailability of the oral dose. In the same study, consuming a high-

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fat meal did not significantly alter the agent's bioavailability, maximum plasma concentration (C_{max}), or half-life when compared with fasting levels.[6] Studies comparing fed and fasted states in plasma area-under-the-curve (AUC) concentrations of sitagliptin and saxagliptin have demonstrated a 20% and 27% increase, respectively, when the drugs are taken with a meal.[7,8] Given the lack of a clinically significant increase with a high-fat meal, both drugs may be taken with or without food.[7,9]

Peak plasma levels of the 100-mg dose of sitagliptin occur approximately one to four hours after oral administration. Peak levels of saxagliptin occur within two hours following the 5-mg dose, with a peak of four hours for its active metabolite. In studies reviewing the pharmacokinetics in various dosages of these agents, the C_{max} and AUC concentration increased in a dose-proportional manner.[7,9]

Distribution. The distribution of sitagliptin and saxagliptin generally depends on a variety of factors, such as plasma protein binding. Both drugs demonstrate low binding to proteins in the serum. Disease states that may alter levels of proteins, therefore, are not expected to lead to wide variations in disposition of these agents.[7,9]

Metabolism. Sitagliptin and saxagliptin differ in the transformation of their original biochemical structures. After ingestion of radiolabeled sitagliptin, approximately 87% was excreted as unchanged drug.[9] Metabolites were detected in low levels, although these are not expected to add to the DPP-4 inhibitory action of sitagliptin. Saxagliptin, however, has a metabolite that retains 50% of the activity of the original compound. Metabolism is mediated primarily by the cytochrome P450 (CYP 450) 3A4/5 system; therefore, inhibitors and inducers of this system are expected to affect the concentration of saxagliptin.[7]

Excretion. Renal and hepatic pathways are involved in the elimination of oral doses of sitagliptin and saxagliptin. After administration of oral carbon 14–labeled sitagliptin, approximately 13% was recovered in the feces and 87% was recovered in the urine.[9] After administration of carbon 14–labeled saxagliptin, percentages of the drug excreted in the urine, as unchanged drug and active metabolites, were 24% and 36%, respectively.[7] Of the administered radioactivity, 22% of saxagliptin was recovered in the feces. Active tubular secretion is involved in the elimination of both agents. The terminal half-life of sitagliptin is approximately 12.4 hours, compared with 2.5 hours for saxagliptin and 3.1 hours for its metabolite.[7,9]

Renal and hepatic insufficiency. Single-dose open-label studies were conducted to evaluate the effect of renal insufficiency on the pharmacokinetics of sitagliptin and saxagliptin.

Renal impairment. Sitagliptin was evaluated in patients with various degrees of renal insufficiency: mild (creatinine clearance [CrCl], 50–80 mL/minute), moderate (CrCl, 30–50 mL/minute), severe (CrCl, less than 30 mL/minute), and end-stage renal disease. Patients with mild renal insufficiency had less than a two-fold increase in plasma AUC levels, compared with control patients who had normal renal function. In patients with moderate and severe renal impairment, including those receiving hemodialysis, plasma AUC levels were increased approximately 2.3 to 4.5 times. This also corresponded to an increased C_{max} and an increased terminal half-life of up to 22.5 hours with severe renal impairment. During hemodialysis, 13.5% of sitagliptin was removed over a three- to four-hour session starting four hours after oral administration.[9,10]

In a study of similar design, saxagliptin was evaluated in patients with various degrees of renal impairment.[7] In this study, however, renal insufficiency did not affect the C_{max} of saxagliptin. In patients with mild renal insufficiency, plasma AUC levels of saxagliptin and its active metabolite were increased 20% and 70%, respectively. The study investigators did not consider this increase to be clinically relevant. In patients

Table 1 Sitagliptin and Saxagliptin: A Product Comparison

	Sitagliptin (Januvia)	Saxagliptin (Onglyza)
Manufacturer	Merck & Co.	Bristol-Myers Squibb/AstraZeneca
Year of approval	2006	2009
Usual dosage	100 mg/day orally	2.5–5 mg/day orally
Contraindications	History of hypersensitivity	None
Dose adjustments	*Moderate renal insufficiency:* CrCl ≥ 30–50 mL/minute; serum creatinine between 1.7 and 3 mg/dL (men) or between 1.5 and 2.5 mg/dL (women) ➔ 50 mg orally daily *Severe renal insufficiency:* CrCl < 30 mL/minute; serum creatinine >3 mg/dL (men) or >2.5 mg/dL (women), or if patient is receiving dialysis ➔ 25 mg orally daily	*Moderate or severe renal insufficiency or end-stage renal disease:* (CrCl ≤ 50 mL/minute) ➔ 2.5 mg orally daily Strong CYP 450 3A4/5 inhibitors: 2.5 mg orally daily
Common adverse reactions	Upper respiratory tract infection, nasopharyngitis, headache	Upper respiratory tract infection, urinary tract infection, headache
Cost (30-day supply)	$206.94 (drugstore.com, as of August 24, 2010)	$203.09 (drugstore.com, as of August 24, 2010)

CrCl = creatinine clearance; CYP 450 = cytochrome P450.
From Onglyza and Januvia package inserts.[7,9]

with moderate and severe renal impairment, plasma AUC levels were noted to be 2.1 and 4.5 times higher than values in patients with normal renal function.[7] Given the alterations in pharmacokinetics in moderate and severe renal impairment, dosage adjustments are recommended for both drugs.

Hepatic impairment. Migoya et al. conducted an open-label, single-dose study of patients with moderate hepatic insufficiency with sitagliptin 100 mg. The increases in AUC concentrations and C_{max}, although higher at 21% and 13% respectively, were not judged to be clinically significant. Based on these findings, dose adjustments for sitagliptin are not recommended in mild and moderate hepatic impairment. This agent has not been evaluated in severe hepatic insufficiency.[11]

Following a 10-mg dose of saxagliptin in patients with hepatic impairment of varying degrees (Child-Pugh classes A, B, and C), differences in AUC level and C_{max} of both the drug and metabolite were not found to be clinically meaningful.[7] Dose modifications of saxagliptin are not recommended for patients with hepatic insufficiency.[7]

DRUG–DRUG INTERACTIONS

On the basis of the limited hepatic metabolism of sitagliptin, clinically significant drug interactions are not expected. Saxagliptin metabolism, however, involves the action of CYP 450 isoenzymes 3A4/5, leading to the potential for interactions with inhibitors and inducers of this system. *In vivo* studies of the effect of saxagliptin on the pharmacokinetics of metformin, glyburide (DiaBeta, Sanofi-Aventis), pioglitazone (Actos, Takeda/Lilly), digoxin (Lanoxin, GlaxoSmithKline), simvastatin (Zocor, Merck), diltiazem (e.g., Cardizem, Abbott; Tiazac, Forest), and ketoconazole (Nizoral, Janssen) demonstrate a lack of effect.[7] In a review of the effect of other agents on saxagliptin, the concomitant administration of ketoconazole, a strong inhibitor of the CYP 450 3A4/5 and P-glycoprotein systems, leads to an increase in the C_{max} and AUC level of saxagliptin, with a related decrease in the C_{max} and AUC level of its metabolite. This effect has also been seen with diltiazem, a moderate inhibitor of the CYP 450 3A4 system. A dose reduction of 50% is recommended when saxagliptin is used with strong CYP 450 3A4/5 inhibitors. Additional monitoring or alternative agents may be necessary when moderate inhibitors are used with saxagliptin.[7]

PHARMACODYNAMICS

In evaluations of the physiological effects of sitagliptin and saxagliptin, the percentages of DPP-4 inhibition, as well as the increase in GLP-1 levels, are often reported. In two studies of sitagliptin given in a range of doses in healthy volunteers, dose-dependent inhibition of DPP-4 activity occurred. The difference in inhibition, compared with placebo, was more than 80% for 100 mg over a 24-hour period. Average postprandial active GLP-1 levels were also significantly higher for sitagliptin than for placebo.[12] In patients with type-2 diabetes, similar results were noted with 80% inhibition of plasma DPP-4 activity 24 hours after oral administration as well as up to a two-fold increase in GLP-1 levels.[13] Similarly, in studies of healthy and diabetic patients, plasma DPP-4 levels were inhibited by 50% for saxagliptin 2.5 mg. Postprandial GLP-1 levels were increased 1.5-fold to three-fold, compared with placebo.[14]

CLINICAL EFFICACY

Sitagliptin and saxagliptin have been studied in the treatment of type-2 diabetes as monotherapy and in conjunction with other antidiabetic medications. In placebo-controlled trials, these agents, when used as monotherapy, decreased HbA_{1c} values by 0.6% to 0.9% and were not associated with fluctuations in weight or alterations in lipids; they were associated with an incidence of hypoglycemia similar to that of placebo.[7,9,15]

Sitagliptin in combination with a sulfonylurea or insulin has been associated with additive hypoglycemic effects.[9] Saxagliptin, in combination with insulin, has not been studied; hypoglycemia is more common when saxagliptin is combined with a sulfonylurea as well.[7] No clinical trials to date have assessed the efficacy of sitagliptin or saxagliptin at reducing macrovascular complications associated with type-2 diabetes.

Sitagliptin Trials

Sitagliptin has been evaluated for use in combination with other agents for type-2 diabetes, including metformin, pioglitazone, rosiglitazone (Avandia, GlaxoSmithKline), glimepiride (Amaryl, Sanofi-Aventis), and insulin.

Sitagliptin/metformin. Charbonnel et al. conducted a 24-week, randomized, double-blind, placebo-controlled trial to assess the addition of sitagliptin 100 mg/day to metformin therapy for patients with mild-to-moderate hyperglycemia (mean baseline HbA_{1c}, 8%).[16] In this study, sitagliptin was associated with the following significant reductions:

- HbA_{1c}: least-squares change in mean HbA_{1c} from baseline, –0.65% for sitagliptin vs. –0.02% for placebo ($P < 0.001$)
- fasting plasma glucose (FPG): least-squares mean change from baseline, –16.2 mg/dL for sitagliptin vs. 9 mg/dL for placebo ($P < 0.001$)
- postprandial plasma glucose (PPG) at two hours: least-squares mean change from baseline, –61.3 mg/dL for sitagliptin vs. –10.8 mg/dL for placebo ($P < 0.001$)

Sitagliptin/pioglitazone. A second 24-week, multicenter, randomized, double-blind, placebo-controlled trial was conducted in which sitagliptin was added to pioglitazone therapy.[17] Significant reductions were achieved as follows:

- HbA_{1c}:
  - adjusted mean change from baseline, –0.85% for sitagliptin/pioglitazone; –0.15% for placebo/pioglitazone; and adjusted mean difference from placebo/pioglitazone, –0.70%; 95% confidence interval [CI], –0.85 to –0.54 ($P < 0.001$)
- FPG:
  - adjusted mean change from baseline, –16.7 mg/dL for sitagliptin/pioglitazone; 1 mg/dL for placebo/pioglitazone; and adjusted mean difference from placebo/pioglitazone, –17.7 mg/dL; 95% CI, –24.3 to –11 ($P < 0.001$)

Summary. In both studies,[16,17] sitagliptin was not associated with an increased incidence of hypoglycemia compared with placebo, although the incidence of edema was higher with

sitagliptin/pioglitazone. When sitagliptin was combined with insulin or a sulfonylurea, there was a potentially increased risk of hypoglycemia. Patients should be monitored accordingly.[9]

Saxagliptin Studies

Saxagliptin has been combined with metformin, glyburide, and rosiglitazone or pioglitazone in type-2 diabetes.

Saxagliptin/metformin. In a randomized, double-blind, placebo-controlled, 24-week trial by DeFronzo et al., saxagliptin 2.5 mg, 5 mg, or 10 mg was added to metformin.[18] The combination was associated with a statistically significant decrease in HbA_{1c}, compared with metformin/placebo—adjusted mean change in HbA_{1c} from baseline, –0.59% for saxagliptin 2.5 mg/metformin, –0.69% with saxagliptin 5 mg/metformin, and –0.58% with saxagliptin 10 mg/metformin vs. 0.13% with placebo/metformin ($P \leq 0.0001$ for all saxagliptin groups).[18]

Compared with patients receiving metformin/placebo, more patients using saxagliptin/metformin achieved HbA_{1c} values below 7% (difference vs. placebo [95% CI], 20.5% (10.6–30.5), 27% (17–36.7), and 27.9% (17.7–37.7 [$P < 0.0001$ for all groups]).

FPG levels were also decreased; adjusted mean changes in FPG from baseline were –14.3 mg/dL for saxagliptin 2.5 mg/metformin; –22.0 mg/dL for saxagliptin 5 mg/metformin; and –20.5 mg/dL for saxagliptin 10 mg/metformin vs. 1.2 mg/dL for placebo/metformin ($P \leq 0.0001$ for all saxagliptin groups).

Saxagliptin/thiazolidinedione (TZD). A second 24-week, randomized, multicenter, double-blind, placebo-controlled, phase 3 study was conducted by Hollander et al. to compare the effects of adding saxagliptin 2.5 mg and 5 mg to either pioglitazone or rosiglitazone therapy.[19] The combination was associated with the following significant reductions:

- HbA_{1c}:
  - adjusted mean change from baseline, –0.66% with TZD/saxagliptin 2.5 mg ($P = 0.0007$)
  - adjusted mean change from baseline, –0.94% with TZD/saxagliptin 5 mg ($P < 0.0001$)
  - adjusted mean change from baseline, –0.3% with TZD/placebo
- FPG:
  - adjusted mean change from baseline, –14.4 mg/dL with TZD/saxagliptin 2.5 mg ($P = 0.053$)
  - adjusted mean change from baseline, –18 mg/dL with TZD/saxagliptin 5 mg ($P = 0.0005$)
  - adjusted mean change from baseline, –3.6 mg/dL with TZD/placebo

Saxagliptin/glyburide. A third 24-week, randomized, multicenter, double-blind trial was designed by Chacra et al. to assess the efficacy of saxagliptin 2.5 mg or 5 mg in combination with glyburide, titrated to a maximum dose of 15 mg, compared with glyburide alone.[20] At week 24, saxagliptin 2.5 mg or 5 mg showed these reductions:

- HbA_{1c}: adjusted mean change from baseline, –0.54% for saxagliptin 2.5 mg and –0.64% for 5 mg vs. 0.08% for upwardly titrated glyburide ($P < 0.0001$ for both)
- FPG: adjusted mean change from baseline, –7 mg/dL for saxagliptin 2.5 mg ($P = 0.0218$) and –10 mg/dL for 5 mg ($P = 0.002$), versus 1 mg/dL for placebo, compared with glyburide alone.

Summary. In each of these trials,[18–20] the proportion of patients achieving HbA_{1c} values below 7%, (the current goal recommended by the American Diabetes Association[21]) was greater when therapy included saxagliptin compared with placebo.

SAFETY AND ADVERSE EFFECTS

The most common adverse reactions occurring in 5% of patients or more who received DPP-4 inhibitors were upper respiratory tract infection, nasopharyngitis, and headache with sitagliptin and upper respiratory tract infection, urinary tract infection, and headache with saxagliptin. The incidence of hypoglycemia is reportedly increased when sitagliptin is used with a sulfonylurea or insulin; the risk is increased when saxagliptin is used with a sulfonylurea.[7,9] Although the risk of hypoglycemia has not been studied, it is probably increased with the combined use of saxagliptin and insulin as well. In patients with renal impairment, dosage adjustments are also necessary to minimize the potential for hypoglycemia.

Other adverse events that have been identified from postmarketing reports of sitagliptin include serious allergic reactions, including anaphylaxis, angioedema, and Stevens–Johnson syndrome. Sitagliptin is contraindicated in individuals with hypersensitivity to any of the components of the formulation.[9] Sitagliptin should be used with caution in patients who have a history of pancreatitis. There have been reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, with sitagliptin use. Sitagliptin has not been studied in patients with a history of pancreatitis. It is prudent to monitor patients for signs and symptoms of pancreatitis and to discontinue sitagliptin if pancreatitis is suspected.[22]

INDICATIONS

Sitagliptin and saxagliptin are approved, along with diet and exercise, for the treatment of type-2 diabetes in adults.[7,9] These agents should not be used in individuals with type-1 diabetes or in people with diabetic ketoacidosis. Sitagliptin has been studied in combination with insulin therapy, whereas saxagliptin has not.

CONTRAINDICATIONS

Sitagliptin has been associated with severe hypersensitivity reactions, including anaphylaxis, angioedema, and Stevens–Johnson syndrome. This agent is contraindicated in individuals with sensitivity to sitagliptin or any of its components.[9] Sitagliptin has been associated with postmarketing reports of pancreatitis. Caution should be used in individuals with a history of pancreatitis; sitagliptin should be discontinued if pancreatitis is suspected. Although there are no data to suggest that pancreatitis is a class effect of these agents at this time, it would be prudent to discontinue saxagliptin as well if pancreatitis is suspected.

For patients with renal insufficiency, dosage adjustments are required for both sitagliptin and saxagliptin to minimize the risk of hypoglycemia. It is important to monitor renal function, in addition to glycemic control, after initiating therapy.

COST AND ECONOMIC BURDEN

Diabetes represents a leading cause of death in the U.S.[25] This chronic disease is associated with more than $174 billion in costs to the health care system in the U.S. Average medical expenses for treating diabetic patients are about 2.3 times higher than expenses for patients without diabetes.[1] Given these findings, the continued development of cost-effective agents and treatment options is critical in order to curb health care costs associated with this disease.

DPP-4 inhibitors have been studied in combination with other agents, and they have had a favorable effect on glucose control. These agents are associated with a modest effect on HbA_{1c} values, but their utility may be limited because of their cost (approximately $200 for a 30-day supply of either agent) when compared with older, generic medications. Long-term safety and efficacy data are needed before these agents can be considered a preferred treatment in diabetes.

CONCLUSION

Although sitagliptin and saxagliptin are both approved as adjunctive therapies to diet and exercise in type-2 diabetes, current data suggest that metformin or a sulfonylurea is generally necessary as a first-line treatment for significantly lowering blood glucose levels.[23] The potential benefits of DPP-4 inhibitors include their complementary mechanism of action with other antidiabetic medications, a favorable adverse-effect profile, and a neutral effect on weight. With a low risk of hypoglycemia, sitagliptin and saxagliptin are advantageous for patients who are close to their target HbA_{1c} but who continually experience elevated glucose levels after meals. As to the advantages of selecting one DPP-4 inhibitor over another, comparative clinical data are unavailable. Specific characteristics of these agents (i.e., dose adjustments for renal impairment, drug interactions), as well as future clinical experience and trial data, will serve as a guide for selection.[24]

Identifying appropriate patients for DPP-4 therapy should include an evaluation of the cost, the risk of hypoglycemia, and the modest treatment effect associated with this drug class. Other DDP-4 inhibitors, including vildagliptin (Galvus, Novartis) and alogliptin (Takeda), are currently in development.

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