New Drug

Sitagliptin Phosphate: A DPP-4 Inhibitor for the Treatment of Type 2 Diabetes Mellitus

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ABSTRACT

Background: Sitagliptin phosphate, the first dipeptidyl peptidase 4 (DPP-4) inhibitor, provides a new treatment option for patients with type 2 diabetes.

Objective: The purpose of this article is to review the pharmacology, pharmacokinetics, pharmacodynamics, clinical efficacy, adverse effects, and cost of sitagliptin in adults with type 2 diabetes.

Methods: A literature search of MEDLINE (1966–May 10, 2007), Iowa Drug Information Service (1966–May 10, 2007), and International Pharmaceutical Abstracts (1970–May 10, 2007) was performed using the terms *sitagliptin* and *MK-0431*. English-language, original research and review articles were reviewed, as were citations from these articles. The 2005 and 2006 American Diabetes Association Scientific Abstracts were searched, and the US Food and Drug Administration review of the new drug application for sitagliptin and select information from the manufacturer were consulted.

Results: By inhibiting DPP-4, sitagliptin enhances postprandial levels of active glucagon-like peptide-1 (GLP-1), leading to a rise in insulin release and decrease in glucagon secretion from pancreatic α-cells. Sitagliptin is 87% orally bioavailable, undergoes minimal hepatic metabolism, and is primarily excreted unchanged (~79%) in the urine. At doses ≥100 mg QD, DPP-4 activity is inhibited by >80%, with a consequent 2-fold rise in active GLP-1 levels. The reduction in glycosylated hemoglobin (HbA_{1c}) observed with 100 mg QD of sitagliptin in Phase III monotherapy trials ranged from ~0.5% to 0.6% ($P \leq 0.001$ vs placebo). In Phase III combination trials, HbA_{1c} was reduced by ~0.7% when added to metformin and ~0.9% with pioglitazone ($P < 0.001$ vs placebo). Markers of β-cell function, including proinsulin/insulin ratio and homeostasis model assessment of β-cell function, were improved with sitagliptin treatment. In studies, sitagliptin has been well tolerated; significant hypoglycemia and weight gain have not been noted.

Conclusions: When used alone or in combination with metformin or pioglitazone, sitagliptin has been associated with significant reductions in HbA_{1c} and has been well tolerated. Before its place in therapy can be firmly established, long-term studies evaluating the safety of prolonged DPP-4 inhibition are necessary. (*Clin Ther*. 2007;29:2614–2634) Copyright © 2007 Excerpta Medica, Inc.

Key words: sitagliptin, MK-0431, type 2 diabetes, dipeptidyl peptidase-4.

INTRODUCTION

It is estimated that >180 million people worldwide have diabetes mellitus; this figure is expected to more than double by the year 2030.[1] In the United States alone, 7% of the population (20.8 million) has diabetes mellitus, including 1.5 million newly diagnosed cases in people ≥20 years of age in 2005.[2] Although typically associated with older age, type 2 diabetes—the most prevalent type, accounting for 90% to 95% of all cases—is also now being diagnosed in children and adolescents.[2]

The increasing prevalence of diabetes is of concern because of the morbidity and mortality associated with the disease. Complications of uncontrolled type 2 diabetes include cardiovascular disease and microvascular complications, such as peripheral neuropathy,

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nephropathy, and retinopathy. These life-threatening complications have made diabetes the fifth-leading cause of death in the United States[2] and accounted for US $24.6 billion of the $92 billion of direct medical expenditures attributed to the disease in 2002.[3]

The societal and economic burdens of type 2 diabetes highlight the importance of tight glycemic control and prevention and management of diabetic complications. In addition to lifestyle modifications, several classes of pharmacologic agents are available that lower blood glucose levels by various mechanisms of action. These include α-glucosidase inhibitors, biguanides (eg, metformin), meglitinides, sulfonylureas, thiazolidinediones, insulin, amylin agonists (eg, pramlintide), and glucagon-like peptide-1 (GLP-1) analogues (eg, exenatide).[4] The glucose-lowering effectiveness of each of these antidiabetic interventions, when used as monotherapy, varies, as described in a consensus statement on the management of hyperglycemia in patients with type 2 diabetes developed by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (**Table I**).[4]

In October 2006, the US Food and Drug Administration (FDA) approved sitagliptin phosphate* for use as monotherapy or in combination with metformin or thiazolidinediones to improve glycemic control in patients with type 2 diabetes in conjunction with diet and exercise.[5] Sitagliptin was the first agent worldwide in a new class of medications called *dipeptidyl peptidase-4 (DPP-4) inhibitors*, providing a new oral therapeutic option. The purpose of this article is to review the pharmacology, pharmacokinetics, pharmacodynamics, clinical efficacy, adverse effects, and cost of therapy of sitagliptin phosphate in adult patients with type 2 diabetes mellitus.

MATERIALS AND METHODS

A literature search of MEDLINE (1966–May 10, 2007), Iowa Drug Information Service (1966–May 10, 2007), and International Pharmaceutical Abstracts (1970–May 10, 2007) was performed using the search terms *sitagliptin* and *MK-0431*. English-language, original research articles and review articles were identified and evaluated. Citations from these articles were also reviewed. Using the same search terms, the 2005 and 2006 ADA Scientific Abstracts were also searched for pertinent abstracts. The FDA review of the new drug application (NDA) for sitagliptin was also consulted, as was select information provided by the manufacturer.

*Trademark: Januvia® (Merck & Co. Inc., Whitehouse Station, New Jersey).

Table I. Glycemia-lowering effectiveness of antidiabetic interventions used as monotherapy in patients with type 2 diabetes mellitus.

Intervention	Expected Decrease in HbA_{1c}, %
Lifestyle modifications to decrease weight and increase activity	1–2
α-Glucosidase inhibitors	0.5–0.8
Metformin	1.5
Meglitinides	1–1.5
Sulfonylureas	1.5
Thiazolidinediones	0.5–1.4
Insulin	1.5–2.5
Pramlintide	0.5–1.0
Exenatide	0.5–1.0

HbA_{1c} = glycosylated hemoglobin.
Adapted with permission.[4]

CLINICAL PHARMACOLOGY

Sitagliptin phosphate is chemically described as 7-[(3*R*)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazine phosphate (1:1) monohydrate. The compound has a molecular weight of 523.32 Da and a molecular formula of $C_{16}H_{15}F_6N_5O \cdot H_3PO_4 \cdot H_2O$. The chemical structure is depicted in the **figure**.

Mechanism of Action

Sitagliptin enhances the effects of the incretin hormones glucose-dependent insulinotropic peptide (also known as *gastric inhibitory polypeptide [GIP]*) and GLP-1. Secreted in the intestine in response to food, GIP and GLP-1 have a role in the regulation of glucose homeostasis. Activation of GIP and GLP-1 receptors on pancreatic β-cells leads to increased levels of cyclic adenosine monophosphate and intracellular calcium, with subsequent glucose-dependent insulin secretion.[6] In addition, sustained receptor activation is associated with insulin biosynthesis and stimulation of β-cell proliferation.[6] Animal and in vitro data fur-

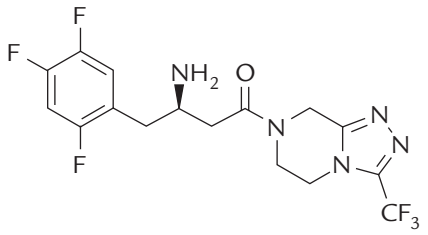

Figure. Chemical structure of sitagliptin. Reprinted with permission.[10]

ther suggest that activation of GIP and GLP-1 receptors promotes β-cell resistance to apoptosis, proliferation, and neogenesis, resulting in enhanced β-cell function.[6,7] Additional functions of GLP-1 include inhibition of glucagon secretion from pancreatic α-cells, resulting in decreased hepatic glucose production; slowing of gastric emptying; suppression of food intake; and enhancement of glucose disposal via neural mechanisms.[6,7]

In patients with type 2 diabetes, the response to the incretin hormones is defective, largely because the insulinotropic activity of GIP, but not GLP-1, is attenuated.[6] Data suggest that there is also a statistically significant decline in meal-stimulated GLP-1 levels in patients with type 2 diabetes compared with those with normal glucose tolerance (mean [SD], 2482 [145] vs 3101 [198] pmol/L/240 min; $P = 0.024$).[8] Exogenous administration of GLP-1, therefore, would in theory appear to be an attractive therapeutic modality for type 2 diabetes. This approach, however, is limited by the rapid inactivation of the incretin hormones by the DPP-4 enzyme, which preferentially cleaves substrates that have a proline or alanine in the penultimate position.[9] In addition to and independent of its enzymatic activity in plasma, DPP-4 is a membrane-spanning peptidase that is widely distributed in numerous tissues and T-cells, B-cells, and natural killer cells.[7] Also known as *CD26*, DPP-4 serves as a T-cell costimulator, playing a functional role in T-cell activation and proliferation.[7,9]

Two viable methods to enhance GLP-1 effects in vivo include administration of agents that mimic the effects of the incretins but are resistant to degradation by DPP-4 (eg, exenatide) and agents that prevent incretin degradation. Sitagliptin exerts its therapeutic effect via the latter mechanism. Thus, following administration of sitagliptin, postprandial levels of active GLP-1 are increased and activity is prolonged, with a resultant rise in insulin release and decrease in glucagon secretion from the pancreatic α-cells.[5]

Sitagliptin is a potent, reversible competitive inhibitor of DPP-4. Results from in vitro studies that evaluated the DPP-4 inhibitory properties of sitagliptin, among other compounds, have suggested that sitagliptin exhibits high selectivity for DPP-4 (IC_{50}, 18 nM). Affinity for other proline-specific peptidases, DPP-8 (IC_{50}, 48,000 nM) and DPP-9 (IC_{50}, >100,000 nM), is low.[10] Low affinity for these peptidases is of particular importance since in preclinical studies, inhibition of DPP-8 and DPP-9 has been associated with severe toxicities, including alopecia, blood dyscrasias, multiorgan histopathologic changes, and mortality in rats; gastrointestinal toxicity in dogs; and attenuation of T-cell function in human in vitro models.[11] Notably, the effects on the immune system were not seen with a DPP–4-selective compound.[11] Likewise, whereas other nonselective DPP-4 inhibitors have been associated with the development of necrotic skin lesions in preclinical studies involving monkeys, no treatment-related skin toxicity was observed in a 3-month study in monkeys treated with sitagliptin (personal communication, Carol Teutsch, MD, Merck & Co. Inc., September 7, 2007).

Pharmacokinetics

Several studies characterizing the pharmacokinetic properties of sitagliptin in animals, healthy subjects, and patients with type 2 diabetes have been published.[10,12–17] Key pharmacokinetic parameters in healthy subjects, as provided by the manufacturer,[5] are summarized in **Table II**. In general, the pharmacokinetics of sitagliptin in healthy subjects are comparable with those observed in patients with type 2 diabetes.[5,14,17]

Following administration of an oral 100-mg dose in healthy volunteers, sitagliptin was rapidly absorbed, with a median T_{max} of 1 to 4 hours.[5] Plasma AUC was 8.52 μM · h and C_{max} was 950 nM.[5] Sitagliptin plasma AUC has been found to be increased in an approximate dose-dependent manner in both single-dose (1.5–600 mg)[14] and multiple-dose (25–600 mg QD and 300 mg BID)[15] studies in healthy volunteers, whereas C_{max} increased in a slightly greater than dose-proportional manner. The administration of a high-fat breakfast prior to a single oral 25-mg dose of sitagliptin has not been found to influence the plasma

Table II. Pharmacokinetic parameters of sitagliptin in healthy subjects.[5]

Parameter	Value
Bioavailability	87%
Volume of distribution	~198 L
Protein binding	38%
T_{max}	1–4 h
Metabolism	Minimal hepatic metabolism
Elimination	87% Urine (~79% unchanged); 13% feces
Apparent terminal $t_{1/2}$	~12.4 h
Renal clearance	~350 mL/min

$AUC_{0-\infty}$; the ratio of the least-squares (LS) mean (95% CI) ratio (fed/fasted) was 1.01 (0.94–1.10).[14] An increase in C_{max} of ~20% was observed in the fed state; however, this difference was not statistically significant versus that observed in the fasting state (LS mean ratio, 1.21 [95% CI, 1.00–1.45]).[14] Since no pharmacokinetic parameters are appreciably influenced by food, sitagliptin may be dosed without regard to meals.[5] Steady-state concentrations of sitagliptin are achieved within 2 to 3 days of administration.[15,16] The mean volume of distribution of sitagliptin, as determined after administration of a single 100-mg IV dose in healthy subjects, is ~198 L, and 38% of the drug is reversibly bound to plasma proteins.[5]

Sitagliptin does not appear to undergo extensive metabolism. Data from a study by Vincent et al[13] evaluating the metabolism and excretion of [^{14}C]sitagliptin in 6 healthy male subjects suggest that after a single oral dose, the parent drug comprised the majority of plasma (78%–90%) and urinary (~84%–88%) radioactivity. Six metabolites (M1–M6) were detected in small amounts, each comprising <1% to 8% of the circulating plasma radioactivity and <1% to 5% of total urinary radioactivity. In vitro experiments found that cytochrome P450 (CYP) isozyme 3A4, and to a lesser extent CYP2C8, were the major isozymes associated with the limited sitagliptin metabolism.[13] Due to the low levels in plasma and low affinity for the DPP-4 enzyme (M1, M2, and M5 were tested for DPP-4 inhibition and found to be ~300-, 1000-, 1000-fold less active, respectively, than the parent drug),[13] the metabolites are not believed to contribute to the pharmacologic activity of sitagliptin.[5,13,18] In the same study, the majority (87%) of the radioactive dose was recovered in the urine within 1 week of dosing; 13% of the administered dose was excreted via the feces.[13]

The apparent terminal $t_{1/2}$ of sitagliptin is ~12.4 hours. Both the fraction of the oral dose excreted unchanged in the urine (~79%) and the renal clearance (Cl_R (~350 mL/min) are independent of dose.[14,15] Sitagliptin undergoes active tubular secretion, as evidenced by the fact that Cl_R exceeds creatinine clearance (CrCl).[5] The compound is a substrate for human organic anion transporter 3, the organic anion transporting polypeptide OATP4C1, and the efflux transporter P-glycoprotein.[19]

Special Populations

In a single-dose open-label study, Bergman et al[20] evaluated the effects of varying degrees of renal impairment on the pharmacokinetics of sitagliptin. Thirty otherwise healthy participants (18–75 years of age) with either mild (CrCl, 50–80 mL/min), moderate (CrCl, 30–50 mL/min), or severe (CrCl, <30 mL/min) renal insufficiency, end-stage renal disease (ESRD) receiving hemodialysis, or normal renal function (CrCl, >80 mL/min) were included in the study (6 in each group). Subjects with normal renal function and patients with mild to severe renal insufficiency received a single 50-mg oral dose. Patients with ESRD received a single 50-mg dose of sitagliptin 48 hours prior to their normally scheduled hemodialysis session. To quantify the amount of sitagliptin removed by hemodialysis, patients with ESRD received a second 50-mg dose after a 1-week washout period. Hemodialysis was performed 4 hours postdose. Healthy subjects (n = 145) from 11 other studies were included in the historical control group to supplement the subjects in the study with normal renal function. A <2-fold increase in plasma $AUC_{0-\infty}$ was considered by the investigators to be not clinically meaningful. This assertion was based on the fact that in prior studies,[14,15] sitagliptin was well tolerated in healthy subjects receiving doses of up to 600 mg.[20]

Compared with subjects with normal renal function (n = 151), sitagliptin $AUC_{0-\infty}$ values were 1.6, 2.3, 3.8, and 4.5-fold higher in patients with mild, moderate, and severe renal insufficiency and ESRD, respectively.[20] The geometric LS mean (90% CI) ratios for C_{max} were 1.35 (1.15–1.58) in patients with mild renal insufficiency, 1.43 (1.23–1.67) in patients with

moderate renal insufficiency, 1.75 (1.51–2.03) in patients with severe renal insufficiency, and 1.42 (1.22–1.65) in patients with ESRD. Compared with values in subjects with normal renal function (13.1 hours), the terminal $t_{1/2}$ values of sitagliptin in those with mild, moderate, and severe renal insufficiency and ESRD were 16.1, 19.1, 22.5, and 28.4 hours, respectively ($P = 0.011$ for group with mild renal insufficiency; $P < 0.001$ for all other sitagliptin groups). Cl_R of sitagliptin was approximately proportional to CrCl. The fractions of the sitagliptin dose removed by hemodialysis initiated at 4 and 48 hours postdose were 13.5% and 3.5%, respectively. As reported by the investigators, sitagliptin was well tolerated in all groups, although no specific data on adverse events were provided.[20] In light of these findings, dosage adjustments are recommended in patients with moderate or severe renal insufficiency or ESRD (see Dosage and Administration section).[5] Caution may be needed, however, when prescribing sitagliptin in patients with mild renal impairment, although no dosage adjustment is recommended by the manufacturer.[5]

The effects of moderate hepatic impairment on sitagliptin pharmacokinetics have also been evaluated in a study published only as an abstract.[21] Ten patients with Child-Pugh scores ranging from 7 to 9 and 10 healthy matched controls each received a single 100-mg oral sitagliptin dose in an open-label fashion. The prespecified range of bounds for clinical nonsignificance for the AUC was 0.5 to 2.00. Compared with healthy subjects, ~21% and ~13% increases in mean plasma $AUC_{0-\infty}$ and C_{max}, respectively, were observed in patients with hepatic insufficiency; however, both parameters fell within the prespecified bounds for clinical nonsignificance (actual values not provided). There were no statistically significant differences in T_{max}, apparent terminal $t_{1/2}$, fraction of the oral dose excreted into urine, or Cl_R between the 2 groups. Sitagliptin was well tolerated in both groups.[21] As such, no dosage adjustment is recommended by the manufacturer in patients with moderate hepatic impairment.[5] However, due to the small sample size of the study, more data may be necessary to evaluate the true effect of hepatic impairment on sitagliptin pharmacokinetics. Studies assessing the effects of severe hepatic impairment on sitagliptin pharmacokinetics were not identified in the literature search.

In another study published only as an abstract, the effects of age, sex, and obesity on sitagliptin pharmacokinetics were assessed.[22] Eight healthy, young (age, 18–45 years), nonobese women; 10 healthy, elderly (age, 65–80 years), nonobese men; 10 healthy, elderly, nonobese women; and 10 healthy, young adult, obese (body mass index [BMI], 30–40 kg/m^2) subjects were enrolled in the study. Within each group, 2 participants received placebo, while the others received a single oral 50-mg sitagliptin dose. Pharmacokinetic data from a previous study in which 6 healthy, young, nonobese male subjects received a single oral 50-mg dose of sitagliptin were also included in the analysis.[22]

Pharmacokinetic parameters that were significantly different between groups were as follows. The $AUC_{0-\infty}$ geometric mean ratio (GMRs) (90% CI) comparing elderly and young (pooled across sex) and young male obese and nonobese subjects were 1.31 (1.19–1.43) and 0.77 (0.69–0.86), respectively. The C_{max} GMR (90% CI) comparing elderly and young was 1.23 (1.04–1.46); for the comparison between female and male subjects (pooled across age), GMR (90% CI) C_{max} was 1.46 (1.23–1.73). These differences in plasma pharmacokinetics, however, were not considered by the investigators to be clinically meaningful.[22] Notably, as per the prescribing information, the dose of sitagliptin does not require adjustment for age, sex, or obesity.[5]

In a multicenter, randomized, double-blind, placebo-controlled study, 32 middle-aged (45–65 years), obese (mean BMI, 33.7 kg/m^2 [range, 30.2–39.8 kg/m^2]) subjects received sitagliptin 200 mg BID (n = 24) or placebo (n = 8) for 28 days.[23] Sitagliptin pharmacokinetic parameters were similar to those obtained from single-dose[14] and multiple-dose[15] studies in healthy male subjects. A search of the literature did not yield any studies assessing the use of sitagliptin in the pediatric population.

Pharmacodynamics

In clinical studies involving healthy volunteers, treatment with sitagliptin was associated with dose-dependent inhibition of DPP-4 activity.[14,15] The percentage inhibition of DPP-4 activity that has correlated with near-maximal glucose-lowering effects has been found to be 80% or greater in rodent models.[10] This degree of inhibition has been observed in subjects treated with sitagliptin in pharmacodynamic studies. In a single-dose study (1.5–600 mg), the weighted average inhibition (WAI) of DPP-4 activity was at least 80% with doses ≥50 mg over a 12-hour

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