Vildagliptin: A novel oral therapy for type 2 diabetes mellitus

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Almost 10% of the U.S. population ages 20 years or older has diabetes mellitus, either diagnosed or undiagnosed.1 Despite the availability of many different types of medications to treat type 2 diabetes mellitus, less than one half of patients reach target glycosylated hemoglobin (HbA1c) levels.2 Because of this high prevalence and the difficulty patients experience reaching targets for glycemic control, researchers are actively investigating new agents to improve the management of type 2 diabetes mellitus. Over the past few years, the labeling of a number of new medications for the treatment of diabetes has been approved by the Food and Drug Administration (FDA). These include pramlintide, exenatide, inhaled insulin, insulin glulisine, and insulin detemir.

With the exception of inhaled insulin, none of the other recently approved diabetes medications are administered orally. Although insulin and other injectable therapies are effective treatments, there are often barriers to therapy with injectable medications. Some of these barriers include patient and physician resistance, patients’ fear of needles, inconvenience, the complexity of regimens, time, and cost.3 Because of these barriers to injectable therapy and the increasing incidence of diabetes, more options for oral antidiabetic agents are warranted.

Vildagliptin is among a new class of oral diabetes medications currently being studied. The mechanism of these agents involves inhibition of dipeptidyl peptidase IV (DPP4), the enzyme that contributes to the in-
activation of the hormone glucagon like peptide-1 (GLP-1). This inhibition of DPP4 results in increased levels of active GLP-1. GLP-1 is a hormone secreted by the intestines from L cells, the most abundant endocrine cells in the gut, in response to food. In addition to stimulating insulin production, it is thought that GLP-1 secretion slows gastric emptying, inhibits glucagon secretion, and decreases appetite. GLP-1 secretion is significantly reduced in patients with diabetes in response to meal ingestion compared with persons without diabetes. Lower GLP-1 levels in patients with type 2 diabetes mellitus are thought to be a consequence and not a cause of the disease.

GLP-1 has been studied for many years, but research during the past decade has shed more light on a possible role of GLP-1 in the treatment of type 2 diabetes mellitus. The effect of a subcutaneous continuous infusion of GLP-1 versus saline on glycemic control was evaluated over six weeks in patients with type 2 diabetes mellitus. In the group receiving the GLP-1 infusion, a decrease in HbA\textsubscript{1c} from 9.2% to 7.9% (p = 0.003) was seen, indicating a sustained improvement in glycemic control. In addition, a decrease in mean fasting plasma glucose concentration was observed in the GLP-1 group of 75 mg/dL (4.3 mmol/L) by week 6 (p < 0.0001). From this study, it is evident that GLP-1 can have a significant effect on glucose regulation.

In October 2006, the labeling for sitagliptin (Januvia), a DPP4 inhibitor, was approved by FDA for the treatment of type 2 diabetes mellitus as monotherapy or in combination with metformin or thiazolidinediones. Vildagliptin is not yet approved for marketing in the United States, but the manufacturer announced that it received an approvable letter from FDA in late February 2007. Saxagliptin, another DPP4 inhibitor, is also being investigated. As these novel agents become available for the treatment of type 2 diabetes mellitus, it is important to examine the properties of these drugs. This article reviews the pharmacology, pharmacokinetics, clinical efficacy, drug interactions, and role in therapy of vildagliptin.

**Pharmacology**

Figure 1 displays the chemical structure of vildagliptin, and Figure 2 illustrates the mechanism of action of this drug. Vildagliptin is a selective, reversible, competitive inhibitor of DPP4, an enzyme and binding protein present in many tissues such as the kidneys, liver, brush-border membranes of the intestine, pancreatic duct, lymphocytes, and endothelial cells. Vildagliptin binds to and forms a complex with DPP4, resulting in its inhibition. DPP4 is involved in the inactivation of many neuropeptides, cytokines, chemokines, and gastrointestinal hormones. Two important hormones involved in glucose homeostasis and inactivated by DPP4 are glucose-dependent insulino-tropic poly-peptide (GIP) and GLP-1. GIP and GLP-1 are incretins, which are hormones released from the gut that stimulate insulin secretion in response to food intake. However, GIP does not stimulate insulin release in patients with type 2 diabetes mellitus as it does in patients without diabetes. GLP-1, the most potent insulinotropic hormone, enhances glucose-dependent secretion of insulin from pancreatic β-cells and inhibits glucagon secretion. Inhibition of DPP4, which results in increased levels of active GLP-1, has been shown to be an effective treatment for type 2 diabetes mellitus.

**Pharmacokinetics**

The disposition of vildagliptin has been described in both a preclinical study with healthy volunteers and another study in patients with type 2 diabetes mellitus. Participants in both studies received vildagliptin 100 mg orally; vildagliptin was rapidly absorbed, with a peak plasma vildagliptin concentration observed at one to two hours after the dose was given. Vildagliptin displayed an oral bioavailability of 85% in healthy volunteers, and its pharmacokinetics were not affected by food. An absolute oral bioavailability exceeding 90% and an average clearance rate from plasma of 1.5 L/hr/kg with a volume of distribution of 0.7 L/kg were observed following a 1-µmol/kg oral dose administered to cynomolgus monkeys.

The terminal elimination half-life of vildagliptin is 90 minutes, and the vildagliptin–DPP4 complex exhibits a slow dissociation half-life of 55 minutes. Maximum inhibition of DPP4 activity is seen 30 minutes after a vildagliptin dose, and ≥50% inhibition of DPP4 continues for 10 hours or longer. One clinical trial showed mean ± S.D. DPP4 levels to be 60% ± 5% of baseline 24 hours after a 100-mg dose of vildagliptin (p < 0.001).

Figure 1. Chemical structure of vildagliptin.
Vildagliptin is extensively metabolized, primarily in the liver by hydrolysis, and its major metabolite (known as LAY151) is pharmacologically inactive. The parent drug is minimally metabolized by the cytochrome P-450 (CYP) enzyme system. Vildagliptin is largely excreted in the urine; 18–22% of the amount excreted is unmetabolized drug.

Clinical efficacy

Eight clinical trials evaluated vildagliptin use in patients with type 2 diabetes mellitus. The results of these clinical trials are summarized in Table 1.

Ahren et al. evaluated the effects of vildagliptin (formerly known as LAF237) on DPP4 activity, plasma insulin and glucagon levels, and glucose tolerance over 4 weeks in patients with type 2 diabetes mellitus. Men and infertile women over 30 years of age were included in the study if they met the following criteria: history of diet-controlled type 2 diabetes mellitus for 12 weeks or longer, a mean HbA1c value of 6.3–10%, a mean fasting plasma glucose concentration of 130–180 mg/dL (7.2–10.0 mmol/L), fasting C-peptide concentrations greater than 0.3 nmol/L, and a body mass index (BMI) of 20–32 kg/m². Patients were randomized to receive placebo (n = 19) or vildagliptin 100 mg daily (n = 18) given 30 minutes before breakfast. Patients were instructed to check their blood glucose level if hypoglycemia symptoms occurred. Hypoglycemia was defined as a blood glucose concentration of <45 mg/dL (2.5 mmol/L) or hypoglycemia symptoms regardless of glucose concentration. In patients receiving vildagliptin, significant decreases from baseline compared with placebo were reported in HbA1c (−0.38%; 95% confidence interval [CI], −0.54, −0.21; p < 0.001), fasting plasma glucose concentration (−12.6 mg/dL; 95% CI, −25.4, −1.8; p < 0.037), mean 24-hour glucose concentration (−16.2 mg/dL; 95% CI, −25.2, −9.0; p < 0.0001), and mean 4-hour prandial glucose concentration (−27 mg/dL; 95% CI, −39.6, −4.4; p < 0.001). Significant decreases in postbreakfast glucagon levels also were reported in the vildagliptin group: mean ± standard error (S.E.) peak 30-minute glucagon concentrations of 102 ± 9 pg/mL and 90 ± 7 pg/mL at baseline and after treatment, respectively (p = 0.005). No significant changes were seen in insulin levels in patients receiving vildagliptin; however, a significant reduction in DPP4 activity was observed at both 45 minutes (to 1.9% of baseline activity) and 24 hours (to 60% of baseline activity) after oral ingestion of vildagliptin, and a significant increase in peak 30-minute active GLP-1 levels was observed compared with baseline values (p = <0.001). Body weight was not significantly affected, and no patients reported hypoglycemia.
<table>
<thead>
<tr>
<th>Reference, Study Design</th>
<th>n</th>
<th>Duration (weeks)</th>
<th>Vildagliptin and Comparator Regimen</th>
<th>Change in FPG from Baseline (mg/dL)</th>
<th>Change in Prandial Glucose from Baseline (mg/dL)</th>
<th>Change in Glycosylated Hemoglobin from Baseline (%)</th>
<th>Percentage of Subjects with Hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>23, MC, R, DB, PC</td>
<td>37</td>
<td>4</td>
<td>Vildagliptin 100 mg daily Placebo</td>
<td>−19.8 ± 3.6</td>
<td>−34.2 ± 5.4</td>
<td>−0.53 ± 0.06</td>
<td>0</td>
</tr>
<tr>
<td>25, SC, R, DB, PC</td>
<td>20</td>
<td>4</td>
<td>Vildagliptin 100 mg twice daily Placebo</td>
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<td>21.6 ± 7.2b,c</td>
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<td>0</td>
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<td>26, MC, R, DB, PG</td>
<td>279</td>
<td>12</td>
<td>Vildagliptin 25 mg twice daily Placebo</td>
<td>−7.9 ± 4.5 (n = 51)</td>
<td>−18.5 ± 7.2 (n = 26)</td>
<td>−0.31 ± 0.11 (n = 51)</td>
<td>5.9</td>
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<tr>
<td>27, MC, R, DB, PC</td>
<td>98</td>
<td>12</td>
<td>Vildagliptin 25 mg twice daily Placebo</td>
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<td>−30.6 ± 5.4</td>
<td>−0.6 ± 0.1</td>
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<tr>
<td>28, MC, R, DB, PC</td>
<td>107(12 wk)</td>
<td>71(40 wk)</td>
<td>Vildagliptin 50 mg daily + Metformin 1500–3000 mg/day + placebo</td>
<td>12 wk: −18 ± 5.4 52 wk: −10.8 ± 5.4</td>
<td>NA</td>
<td>12 wk: 0.1 ± 0.1 52 wk: NA</td>
<td>1.9b</td>
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<td>Vildagliptin 50 mg daily + Metformin 1500–3000 mg/day + placebo</td>
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<td>−1 ± 0.2b,c</td>
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<td>30, MC, R, DB, PC</td>
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<td>24</td>
<td>Vildagliptin 50 mg twice daily Rosiglitazone 8 mg daily</td>
<td>NA</td>
<td>NA</td>
<td>−1.1 ± 0.1</td>
<td>0.2</td>
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<td>31, MC, R, DB, PC</td>
<td>256</td>
<td>24</td>
<td>Vildagliptin 50 mg twice daily + insulin Insulin + placebo</td>
<td>NA</td>
<td>NA</td>
<td>−0.5 ± 0.1</td>
<td>26.4</td>
</tr>
</tbody>
</table>

*FPG = fasting plasma glucose, MC = multicenter, R = randomized, DB = double-blind, P = placebo-controlled, SC = single-center, PG = parallel group, NA = not available.

bStatistically significant (defined as p ≤ 0.05).

cRelative to placebo.

dData were not provided for all patients for all result categories.

eTwo hypoglycemic (2/107) episodes occurred during the 12-week time period.
authors concluded that vildagliptin significantly improves glucose control in correlation with glucagon levels after four weeks of treatment with no additional risk of hypoglycemia.

A four-week clinical trial was performed by Mari et al.\textsuperscript{25} to assess the effects of vildagliptin 100 mg twice daily \((n = 9)\) versus placebo \((n = 11)\) on \(\beta\)-cell function by evaluating insulin secretory rates (ISRs), plasma glucose concentrations, and insulin sensitivity in patients ages 30–65 years with type 2 diabetes mellitus not previously treated with medications. C-peptide levels were measured to determine ISRs, as plasma C-peptide is a more accurate measure of insulin secretion compared with serum insulin levels. Although C-peptide and insulin are cosecreted equally by the pancreas, insulin undergoes hepatic extraction and variable peripheral clearance, whereas C-peptide is not extracted by the liver and has a constant peripheral clearance.\textsuperscript{32} In order to determine cell function, ISRs and glucose levels were evaluated using standardized meal testing, a proven measure of \(\beta\)-cell function in both healthy individuals and patients with type 2 diabetes mellitus.\textsuperscript{33,34} Insulin sensitivity was assessed by performing a three-hour glucose tolerance test, a validated index of insulin sensitivity.\textsuperscript{35} This was the first published study comparing the effects of vildagliptin alone versus placebo on \(\beta\)-cell function. Study inclusion requirements were HbA\textsubscript{1c} values between 6.5% and 10%, fasting plasma glucose concentrations between 126 and 180 mg/dL (7–10 mmol/L), and a BMI between 22 and 35 kg/m\textsuperscript{2}. A significant decrease in fasting plasma glucose concentrations and prandial glucose concentrations relative to placebo was reported, with differences in least-square means of –28.8 ± 12.6 mg/dL \((p < 0.05)\) and –21.6 ± 7.2 mg/dL \((p < 0.05)\), respectively. The investigators did not find a significant change in insulin or glucagon levels, but did find an increase in ISR and insulin sensitivity by day 28 of the study in patients receiving vildagliptin. Significant increases in plasma GLP-1 and GIP levels were also observed in the vildagliptin group. The authors stated that the increase in GLP-1 contributed to the increase in \(\beta\)-cell function. Of note, no hypoglycemic events were observed in either group, but three undefined mild adverse events were thought to be related to vildagliptin treatment. The definition of hypoglycemia was not provided.

In a 12-week, double-blind, dose–response study, Ristic et al.\textsuperscript{26} evaluated the effects of vildagliptin on HbA\textsubscript{1c}, safety, and tolerability. Patients were randomized to receive vildagliptin 25 mg once daily \((n = 51)\), vildagliptin 25 mg twice daily \((n = 54)\), vildagliptin 50 mg daily \((n = 53)\), vildagliptin 100 mg daily \((n = 63)\), or placebo \((n = 58)\). The investigators also assessed fasting plasma glucose concentrations, prandial glucose concentrations, HbA\textsubscript{1c}, insulin levels, proinsulin levels, and \(\beta\)-cell function. Insulin resistance and \(\beta\)-cell function were evaluated using homeostasis model assessments, which compare a patient’s fasting glucose level and the predicted glucose level based on a computerized model.\textsuperscript{36} Patients were required to meet the following inclusion criteria: HbA\textsubscript{1c} between 6.8% and 10%, fasting plasma glucose concentrations between 110 and 270 mg/dL (6.1–15 mmol/L), and a BMI of 20–42 kg/m\textsuperscript{2}. Reductions in HbA\textsubscript{1c} were seen with all dosages of vildagliptin relative to placebo; however, the reductions in HbA\textsubscript{1c} were statistically significant only in patients receiving vildagliptin 50 mg daily and vildagliptin 100 mg daily with reductions of 0.43% (95% CI, –0.71%, –0.15%; \(p = 0.003)\) and 0.4% (95% CI, –0.68%, –0.13%; \(p = 0.004)\), respectively. All of the vildagliptin dosage regimens resulted in decreased four-hour prandial glucose levels compared with placebo; however, only the 50-mg daily regimen reached statistical significance with a mean ± S.E. change of –25 ± 9.7 mg/dL \((p = 0.012)\). A statistically significant increase in fasting C-peptide levels was observed in patients receiving the vildagliptin 25-mg twice-daily regimen. All groups showed an increase in \(\beta\)-cell function, but this was only statistically significant in patients receiving vildagliptin 100 mg daily. Adverse events were reported in all vildagliptin groups and in the placebo group. The rate of hypoglycemia (defined as a blood glucose concentration of <67 mg/dL [3.7 mmol/L] with or without symptoms) in each vildagliptin group was similar to placebo. Headache was reported more often in patients receiving vildagliptin than placebo. None of the serious adverse events that occurred (urosepsis, acute coronary syndrome, appendicitis, thrombosis, and chest pain) were thought to be related to the study drug. There were no significant changes in body weight among the groups. Cholesterol levels were largely unchanged; however, a small, but significant, decrease in high-density-lipoprotein (HDL) levels was observed in the vildagliptin 100-mg daily group. The authors concluded that vildagliptin was well tolerated, vildagliptin dosages of 50–100 mg daily produced a significant decrease in HbA\textsubscript{1c} over a 12-week time period, and higher vildagliptin dosages may be associated with improved \(\beta\)-cell function.

Vildagliptin was evaluated by Pratley et al.\textsuperscript{27} as monotherapy over 12 weeks in patients with type 2 diabetes mellitus previously controlled by diet modifications. Patients at least 30 years of age with a fasting plasma glucose concentration of 110 and 270 mg/dL (6.1–15 mmol/L), an HbA\textsubscript{1c} between 6.8% and 11%, and a BMI of 20–40 kg/m\textsuperscript{2} were included and randomized to receive vildagliptin 25 mg twice daily \((n = 70)\) or placebo \((n = 28)\). Vildagliptin significantly decreased HbA\textsubscript{1c} fasting plasma glucose levels, and four-hour prandial glucose levels
Vildagliptin

with between-group differences of 
–0.6% ± 0.2% (p = 0.0012), –19.8 ± 7.2 mg/dL (p = 0.0043), and –34.2 ± 9 mg/dL (p = 0.0001), respectively. Greater decreases in HbA1c values were seen in patients with higher (8–9%) baseline HbA1c values (between-group difference of –1.0% ± 0.2%, p = 0.0012). There were no significant between-group differences in body weight, and vildagliptin had no effect on lipid levels. Standard meal tests, used to assess insulin secretion and action, revealed a significant increase in four-hour mean C-peptide levels, a significant increase in corrected insulin response at peak glucose levels, and a significant decrease in four-hour mean glucose levels in the vildagliptin group compared with placebo. The incidence of adverse effects was higher in patients receiving placebo (71.4%) than that in patients receiving vildagliptin (55.7%).

Adverse events that occurred more frequently in the vildagliptin group compared with the placebo group included dizziness, headache, hypertension (not thought to be drug related), and increased sweating. Only one patient in the vildagliptin group developed hypoglycemia, defined as hypoglycemia symptoms and a blood glucose concentration of ≤56 mg/dL (3.1 mmol/L); this episode was attributed to delayed timing of a meal. All of the adverse events were classified as mild or moderate in severity. Despite a relatively small dosage of vildagliptin, significant reductions in HbA1c values, fasting plasma glucose concentrations, and prandial glucose concentrations with no changes in body weight were observed.

The efficacy of vildagliptin 50 mg daily (n = 56) versus placebo (n = 51) was evaluated by Ahren et al.28 in patients with type 2 diabetes mellitus currently treated with metformin. A 12-week treatment period was followed by a 40-week extension in those patients agreeing to continue with the study. The 40-week extension phase continued with 42 patients in the vildagliptin plus metformin group and 29 patients in the placebo plus metformin group. Men and infertile women over 30 years of age were included if they had a diagnosis of type 2 diabetes mellitus for at least six months, been treated with a stable dosage of metformin hydrochloride (1500–3000 mg/day) for at least three months, an HbA1c value of 7–9.5% while receiving metformin, and a baseline BMI of 20–35 kg/m².

The vildagliptin plus metformin group showed a significant HbA1c reduction in the 12- and 52-week time periods, with between-group differences of –0.7% ± 0.1% (p < 0.0001) and –1.1% ± 0.2% (p < 0.0001), respectively. A target HbA1c of <7% was attained by 41.7% of the patients in the vildagliptin plus metformin group, while only 10.7% of patients in the metformin plus placebo group reached this goal after 52 weeks of therapy. In addition, significant decreases in fasting plasma glucose and prandial glucose levels were observed in patients receiving vildagliptin plus metformin at both 12 and 52 weeks, with between-group differences of –21.6 ± 7.2 mg/dL (p = 0.0057) and –9.8 ± 9 mg/dL (p = 0.0312), respectively. A significant decrease in prandial glucose concentrations was also shown at 12 and 52 weeks, with between-group differences of –39.6 ± 7.2 mg/dL (p < 0.0001) and –43.2 ± 10.8 mg/dL (p = 0.0001), respectively. Insulin levels increased in patients receiving vildagliptin plus metformin; however, this increase was significant only in the 40-week extension phase. There were no significant changes in body weight throughout the study period; however, there was a small but significant increase in total cholesterol in the vildagliptin plus metformin group during the extension period. Seven patients experienced a total of 11 episodes of low blood glucose in the vildagliptin plus metformin group; 2 of these episodes, both occurring during the 12-week time period, met the study’s definition of hypoglycemia (symptoms of hypoglycemia and glucose of <56 mg/dL [3.1 mmol/L]). Two other patients receiving vildagliptin plus metformin, one in the 12-week time period and one in the 40-week extension, each had three asymptomatic episodes of low blood glucose (glucose ranges of 38–61 mg/dL [2.1–3.4 mmol/L]). There was total of 12 serious adverse events during the entire study period. Six of these occurred in the vildagliptin plus metformin group, but only 1 serious adverse effect, peripheral edema, was thought to be drug related. This study demonstrated that vildagliptin, when combined with metformin for one year, significantly decreased HbA1c, fasting plasma glucose levels, and prandial glucose levels while increasing insulin levels, with an adverse-effect profile similar to placebo.

The effects of vildagliptin on β-cell function and insulin sensitivity were evaluated over a one-year period. Patients who completed all evaluations over the 52-week study period previously described29 were included (vildagliptin plus metformin, n = 31; metformin plus placebo, n = 26). Beta-cell function was evaluated by calculating an adaptation index, which is thought to be a sensitive parameter for measuring β-cell function.7 A significant decrease was reported in HbA1c and fasting plasma glucose levels, with between-group differences of –1.0% ± 0.2% (p < 0.001) and –16.2 ± 5.4 mg/dL (p = 0.016), respectively. An HbA1c target of <6.5% was reached in 23% of the subjects receiving vildagliptin plus metformin, while none in the metformin plus placebo group reached this goal. The investigators observed a sustained increase in meal-related insulin secretion in patients receiving vildagliptin plus metformin throughout the study period and concluded that vildagliptin in combination with metformin improves
β-cell function in patients with type 2 diabetes mellitus.

A 24-week noninferiority study assessed the efficacy and tolerability of vildagliptin 50 mg twice daily \( (n = 459) \) compared with rosiglitazone 8 mg daily \( (n = 238) \). An adjusted mean ± S.D. change in HbA\(_{1c}\) of –1.1% ± 0.1% was observed in patients receiving vildagliptin, establishing noninferiority to rosiglitazone. A greater reduction in HbA\(_{1c}\) values was seen in both the vildagliptin \( (\text{adjusted mean ± S.D. change of –1.8% ± 0.1%}) \) and the rosiglitazone \( (\text{adjusted mean ± S.D. change of –1.9% ± 0.1%}) \) groups in patients with baseline HbA\(_{1c}\) values exceeding 9%. Decreased total cholesterol levels \( (14\% \text{ decrease, } p < 0.001) \), triglyceride levels \( (9\% \text{ decrease, } p = 0.010) \), and low-density-lipoprotein levels \( (16\% \text{ decrease, } p < 0.001) \) and increased HDL levels \( (5\% \text{ increase, } p = 0.003) \) were observed in the vildagliptin group. In addition, a significant increase in body weight \( (1.6 \text{ kg}) \) was observed in the rosiglitazone group, while no weight changes were seen in patients receiving vildagliptin. One patient in each group reported hypoglycemia, though no definition for hypoglycemia was provided. Vildagliptin 50 mg twice daily was reported to be non inferior to rosiglitazone 8 mg daily for glycemic control in patients with type 2 diabetes mellitus. Patients in the vildagliptin group also had an improvement in lipid levels and no weight gain when compared with rosiglitazone.

A 24-week study evaluated vildagliptin 50 mg twice daily \( (n = 125) \) and placebo \( (n = 131) \) when added to insulin therapy in patients with type 2 diabetes mellitus. Patients were included in the study if they had HbA\(_{1c}\) values of 7.5–11%, required >30 units of insulin per day, and were not taking any oral antidiabetic agents within three months before the study. Insulin dosage adjustments were allowed during the study. A significant reduction in HbA\(_{1c}\) was observed in patients receiving vildagliptin in addition to insulin compared with patients receiving insulin plus placebo. This reduction was even greater in patients over 64 years of age \( (\text{adjusted mean change of –0.7% ± 0.1%}, p < 0.001) \). At the end of the study, there was no difference in the daily insulin dosage required in each group. Hypoglycemia was reported more frequently and was more severe in the insulin plus placebo group when compared with the vildagliptin plus insulin group, though the definition of hypoglycemia was not provided. It was concluded that adding vildagliptin to insulin therapy caused a significant reduction in HbA\(_{1c}\) with less hypoglycemia than treatment with insulin alone.

### Adverse effects and drug interactions

The most common adverse effects reported in patients receiving vildagliptin during clinical trials included headache, nasopharyngitis, cough, constipation, dizziness, and increased sweating. Hypotension was reported in two of the studies of patients receiving vildagliptin, although the cases were not thought to be drug related. The definition of hypoglycemia varied among clinical trials with vildagliptin; however, in most studies, the rate of hypoglycemia observed with vildagliptin was similar to the rate with placebo.

Vildagliptin is not an inducer or an inhibitor of the CYP enzyme system; however, limited data are available regarding drug interactions with vildagliptin. One study reported no pharmacokinetic interaction when glyburide 10 mg daily was given with vildagliptin 100 mg twice daily for 28 days. There was no effect on drug concentrations of glyburide or vildagliptin when used together or as single agents, and no hypoglycemia was reported. Another group of investigators evaluated the safety and pharmacokinetics of the combination of pioglitazone 45 mg daily and vildagliptin 100 mg daily for 28 days. Drug concentrations of pioglitazone and vildagliptin were measured before and during combination therapy. The investigators found no significant change in the plasma concentrations of either drug at any time point, and it was determined that pioglitazone and vildagliptin can be used together safely.

### Dosage and administration

Vildagliptin was evaluated in a dose–response study by Ristic et al., assessing regimens of vildagliptin 25 mg twice daily, 25 mg daily, 50 mg daily, and 100 mg daily. Both vildagliptin 50- and 100-mg dosages led to significant reductions in HbA\(_{1c}\). Significant decreases in HbA\(_{1c}\) fasting plasma glucose levels, and prandial glucose levels were observed with doses of 25 mg twice daily. The highest vildagliptin dosage evaluated in the clinical trials was vildagliptin 100 mg twice daily in patients with type 2 diabetes mellitus; however, HbA\(_{1c}\) values were not assessed for this dosage regimen. Because the labeling for vildagliptin is not yet FDA-approved, dosage recommendations from the manufacturer are not available at this time. However, the drug’s pharmacokinetic properties allow for the possibility of once- or twice-daily dosing.

### Special populations

The effects of hepatic dysfunction on the pharmacokinetics of vildagliptin were studied in patients with normal \( (n = 6) \), mild \( (n = 6) \), moderate \( (n = 6) \), and severe \( (n = 4) \) hepatic dysfunction.
impairment. The levels of severity were not defined. In this open-label study, each patient received a single dose of vildagliptin 100 mg; multiple blood samples were subsequently collected, and concentrations of vildagliptin and its major inactive metabolite were measured. The elimination half-life of vildagliptin was unaffected by hepatic impairment, but the exposure to vildagliptin was increased by 30% in patients with severe hepatic impairment. The maximum plasma vildagliptin concentration and drug exposure were variable among the patients, and no correlation could be made to severity of hepatic impairment. The exposure to the inactive metabolite, however, did correlate with the severity of hepatic impairment. Overall, vildagliptin was safe and well tolerated in patients with mild to moderate hepatic impairment, and the increased exposure to vildagliptin in patients with severe hepatic impairment was not clinically significant. The investigators concluded that no dosage adjustment is warranted when vildagliptin is used in patients with hepatic impairment.

There are no anticipated dosage adjustments required for patients with renal insufficiency.

Role in therapy

Through its inhibition of DPP4, vildagliptin offers a novel treatment option for patients with type 2 diabetes mellitus. Vildagliptin has the advantage of oral administration for patients who are either not candidates for or are resistant to injectable therapies. Many agents used in the treatment of type 2 diabetes mellitus have been associated with weight gain (e.g., thiazolidinediones, sulfonylureas, non-sulfonylurea secretagogues, insulin); however, clinical trials have shown vildagliptin to be weight neutral. The frequency of adverse events, including hypoglycemia, appears to be similar to the rate found with placebo. Vildagliptin was generally shown to have a beneficial or neutral effect on lipid parameters; however, one study reported a small decrease in HDL cholesterol levels, while another found a small increase in total cholesterol.

When used as monotherapy or in combination with metformin or insulin, modest reductions in HbA$_1c$ values (0.4–1.1% reductions) have been observed in patients receiving vildagliptin. In two clinical trials, greater HbA$_1c$ reduction occurred in patients with higher baseline HbA$_1c$ values. Significant reductions in HbA$_1c$ values have been seen as early as 4 weeks after initiation of vildagliptin monotherapy, but even greater reductions have been observed after 12 weeks of treatment. Therefore, it may be advantageous to treat patients with vildagliptin for at least 12 weeks before assessing efficacy.

Type 2 diabetes mellitus is a disease associated with a progressive decline in β-cell function. There are data to suggest that vildagliptin may be associated with improved β-cell function through up to 52 weeks of therapy. The effects of other oral antidiabetic medications on β-cell function are currently being evaluated. The use of thiazolidinediones has been shown to preserve β-cell function in animal models and the effect in humans is currently being studied. The effects of vildagliptin on β-cell preservation and function, as well as the effect of the drug on the progression of type 2 diabetes mellitus, need to be further evaluated. It is possible that the preservation of β-cell function could slow, or stop, disease progression in patients with type 2 diabetes mellitus.

If approved for marketing, vildagliptin should be considered for use as monotherapy or in combination with metformin or insulin in patients with type 2 diabetes mellitus who continue to have mild increases in HbA$_1c$, despite lifestyle modifications and other pharmacologic therapy. Further studies are warranted to evaluate the safety and efficacy of vildagliptin in combination with other antidiabetic agents.

Conclusion

In clinical trials of patients with type 2 diabetes mellitus, vildagliptin has been shown to reduce HbA$_1c$, fasting plasma glucose levels, prandial glucose levels, and prandial glucagon secretion and to improve β-cell function. If vildagliptin is approved for marketing, it will add to the available treatment options for diabetes and will provide patients and health care providers with another noninvasive therapy option.

References


