

Management Strategies for Type 2 Diabetes: Focus on Vildagliptin

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Abstract: The antidiabetic effect of the dipeptidyl peptidase 4 (DPP-4) inhibitors depends on the prolongation of action of the 2 incretin hormones: glucagon like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) by preventing their rapid degradation by the enzyme DPP-4. The use of the DPP-4 inhibitor vildagliptin is associated with mean reduction in glycosylated hemoglobin (HbA_{1c}) levels ranging from 0.5% to 1.0% compared with baseline or placebo. Head-to-head trials show that vildagliptin is less effective than metformin and rosiglitazone, and equally effective to submaximal doses of pioglitazone and glimepiride. The main advantages of vildagliptin are the decreased risk of hypoglycemia, the neutral effect on body weight, the simplicity of use, and reassuring safety profile for up to 2 years. However, its moderate efficacy, the lack of long-term safety and efficacy data, the need for evaluation in patients with renal insufficiency, and relative high cost represent its major limitations. Overall, vildagliptin may be a useful second agent for patients with type 2 diabetes who are not optimally controlled on metformin. This drug can also be used as monotherapy in patients with mild hyperglycemia who cannot tolerate metformin or a sulfonylurea (SU).

Keywords: vildagliptin, DPP-4 inhibitors, diabetes



Introduction

There is general agreement that metformin should be the initial agent for treatment of type 2 diabetes due to its high efficacy and reassuring long-term safety.¹ In addition, it is less likely to cause hypoglycemia, and may cause slight weight loss.¹ Moreover, metformin may decrease the risk of cancer in patients with type 2 diabetes.² Therefore, it was not surprising that experts from the USA and Europe recommended metformin as the initial drug of choice in type 2 diabetes in addition to diet and exercise.¹ Because diabetes is a progressive disease, most patients will eventually require further treatment. Unfortunately, there is no ideal second agent. Sulfonylureas (SUs), the most commonly used second-line treatment, are equally effective to metformin and may be less expensive. However, SUs are associated with hypoglycemia and weight gain.¹ Thiazolidinediones (TZDs) may lead to significant weight gain, fluid retention, increased risk of heart failure, and osteoporosis.¹ The incretin mimetics, exenatide (Byetta) and liraglutide do not generally cause hypoglycemia, and may lead to an average weight loss of approximately 2 kg after 26 weeks of treatment compared with baseline.^{3,4} Meanwhile, these 2 drugs have to be given by injection, can frequently cause nausea and vomiting, and are expensive.^{3,4} While insulin is the most potent anti-diabetic agent, its use is limited by hypoglycemia, weight gain, and requirement of one or more daily injections. In view of the above, there is a need for new drugs that offer a more favorable therapeutic profile. The dipeptidyl peptidase-4 (DPP-4) inhibitors represent a new promising class of anti-diabetic agents with distinct mechanisms of action. This article will focus on the DPP-4 inhibitor vildagliptin (Galvus), which is already approved in Europe for use as an add-on therapy to metformin, TZD, or SU. Vildagliptin is also available in other parts of the world such as Mexico and Brazil.⁵ However, the drug is still under review by the Federal Drug Administration (FDA) in the USA as of the date of writing this article.

Mechanism of Action of Vildagliptin

The mechanism of action of vildagliptin, is based on the effects of the 2 incretin hormones: Glucagon like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide, also called

gastric inhibitory polypeptide, (GIP). These 2 incretins play an important role in glucose homeostasis particularly in the postprandial period. Thus, in response to nutrient intake, GIP (secreted from K cells located in the duodenum and proximal jejunum) and GLP-1 (secreted from L cells located mainly in the ileum) stimulate insulin secretion.³ In fact, it has been recognized long ago that insulin secretion following oral intake of glucose was greater than insulin secretion following intravenous administration of an isoglycemic glucose load.³ The difference between the 2 insulin responses was called the incretin effect.³ In addition to its insulinotropic effect, GLP-1 inhibits postprandial glucagon release, delays gastric emptying, and may promote early satiety, actions that attenuate the increase in blood glucose after meals.³ Therefore, incretin hormones have received much interest to work as drugs for treatment of type 2 diabetes. However, this has not been practically feasible due to their short half-lives, resulting from their rapid inactivation by a protease called DPP-4.³ For instance, the half-life of GLP-1 is only ~2 minutes after intravenous administration.⁶ Vildagliptin is a drug that inhibits DPP-4 and therefore increases the plasma concentrations of native GLP-1 and GIP by approximately 2 fold and prolongs their duration of action. Vildagliptin therefore stimulates insulin secretion and inhibit glucagon release after meals.⁷ However, the drug does not have significant effects on gastric emptying or satiety presumably because the increase in GLP-1 plasma levels is not sufficiently high to exert such actions.⁷

Metabolism and Pharmacokinetics of Vildagliptin

After oral administration, vildagliptin is rapidly absorbed with a bioavailability of ~85% and its maximum plasma concentrations are obtained 1.1 hour post dose.⁸ Food has no significant effect on the drug absorption.⁹ The terminal half-life after oral intake is ~2.8 hours, but the inhibition of DPP-4 lasts ~24 hours after the 100 mg-dose.⁸ Although vildagliptin is metabolized in the liver, there is no evidence that the cytochrome P450 system has an important role in its metabolism making the drug less prone for drug interaction.⁸ The primary route of elimination of vildagliptin is via urinary excretion.⁸



Efficacy of Vildagliptin

Vildagliptin as monotherapy

Vildagliptin was evaluated as monotherapy in several double-blind placebo-controlled trials in drug-naïve patients with type 2 diabetes. The duration of trials lasted up to 112 weeks.¹⁰ The mean decrease in levels of HbA_{1c} was ~0.8% relative to baseline or placebo using the high dosage of 50 mg bid or 100 mg qd.¹¹ However, the drug was less effective when given in a daily dose of 50 mg with HbA_{1c} reduction of ~0.5% vs. baseline.¹¹

Vildagliptin in Combination Therapy (Tables 1 and 2)

Two trials assessed initial treatment of vildagliptin in drug-naïve patients given as monotherapy and in combination with metformin.¹² and pioglitazone¹³ (Table 1). With the high-dose combinations, the average HbA_{1c} reduction was ~1.8% after 24 weeks relative to baseline.^{12,13} However, as shown in Table 1, the efficacy of vildagliptin when used in conjunction with either metformin or pioglitazone was less than additive.^{12,13} In other studies, vildagliptin was used as

Table 1. Overview of trials of vildagliptin used as initial therapy with and without other oral agents.*

Other agent in combination with vildagliptin (reference)	Metformin ¹²	Pioglitazone ¹³
Mean age (years)	53	52
Mean BMI (kg/m ²)	31.2	29
Mean duration of known diabetes (years)	2	2
Mean baseline HbA _{1c} (%)	8.7	8.7
Mean follow-up (weeks)	24	24
Prior diabetes therapy	Drug-naïve	Drug-naïve
Patient groups	4 groups: vildagliptin 50 mg bid + metformin 1000 mg bid (n = 292), vildagliptin 50 mg bid + metformin 500 mg bid (n = 290), vildagliptin 50 mg bid (n = 297), metformin 1000 mg bid (n = 292)	4 groups: pioglitazone 30 mg qd (n = 161), vildagliptin 100 mg qd + pioglitazone 30 mg qd (n = 148), vildagliptin 50 mg qd + pioglitazone 15 mg qd (n = 144), vildagliptin 100 mg qd (n = 153)
Mean HbA _{1c} reduction from baseline	1.8% with vildagliptin + metformin 1000 mg bid, 1.6% with vildagliptin + metformin 500 mg bid, 1.4% with metformin monotherapy, and 1.1% with vildagliptin monotherapy. P < 0.05 for difference between any combination therapy vs. monotherapy. Significance level for difference between metformin monotherapy vs. vildagliptin monotherapy was not mentioned	1.9% with vildagliptin 100 mg qd + pioglitazone 30 mg qd, 1.7% with vildagliptin 50 mg qd + pioglitazone 15 mg qd, 1.4% with pioglitazone 30 mg qd, and 1.1% with vildagliptin 100 mg qd. Both high-dose and low-dose combination are significantly more effective than pioglitazone and vildagliptin monotherapy (P < 0.05). Significance level for difference between pioglitazone monotherapy vs. vildagliptin monotherapy was not mentioned
Mean weight change from baseline	Similar weight loss of -1.2 kg with vildagliptin + metformin 1000 mg bid, and vildagliptin + metformin 500 mg bid, -1.6 kg with metformin monotherapy, and -0.6 kg with vildagliptin monotherapy	Similar weight gain of ~+1.5 kg with pioglitazone monotherapy and low-dose combination, +2.1 kg with the high-dose combination, and no change in weight with vildagliptin monotherapy
Withdrawal due to adverse effects	3.4% with vildagliptin + metformin 1000 mg bid, 2.8% with vildagliptin + metformin 500 mg bid, 4.4% with metformin, and 2.3% with vildagliptin	5.6% with pioglitazone monotherapy, 4.7% with high-dose combination, 5.6% with low-dose combination, and 2.6% with vildagliptin monotherapy

*All trials are randomized, double-blind, and multicenter.

Table 2. Overview of trials of vildagliptin as add-on therapy to other diabetes medications.*

Type of background therapy (reference)	Metformin ¹⁴	Glimepiride ¹⁵	Pioglitazone ¹⁶	Insulin ¹⁷
Mean age (years)	54	58	54	59
Mean BMI (kg/m ²)	31.5	31.3	32.4	33
Mean duration of known diabetes (years)	Not reported	7.1	4.7	14.7
Mean baseline HbA _{1c} (%)	8.5	8.5	8.7	8.4
Mean follow-up (weeks)	24	24	24	24
Background diabetes therapy	Metformin ≥1500 mg/d	Glimepiride 4 mg qd	Pioglitazone 45 mg qd	Insulin (mean dose 82 units/d)
Patient groups	3 groups: vildagliptin 100 mg qAM (n = 125), vildagliptin 100 mg qPM (n = 123), placebo (n = 122)	3 groups: vildagliptin 50 mg qd + (n = 170), vildagliptin 50 mg bid (n = 159), placebo (n = 176)	3 groups: vildagliptin 50 mg qd (n = 147), vildagliptin 50 mg bid (n = 158), placebo (n = 158)	2 groups: vildagliptin 50 mg bid (n = 144) vs. placebo (n = 152)
Mean HbA _{1c} reduction from baseline	0.66% with vildagliptin AM, 0.53% with vildagliptin PM, and an increase of HbA _{1c} 0.17% with placebo. P < 0.05 between either vildagliptin group and placebo group	~0.6% in the 2 vildagliptin groups, no change in HbA _{1c} in the placebo group. P < 0.05 for difference between either vildagliptin group and placebo group	1.0% with vildagliptin 50 mg bid, 0.8% with vildagliptin 50 mg qd, 0.3% with placebo. P < 0.05 between either vildagliptin group and placebo group	0.5% with vildagliptin vs. 0.2% with placebo. P < 0.05 for the difference between the 2 groups
Mean weight change from baseline	Unchanged in the combined vildagliptin group (+0.06 kg), and -0.7 kg with placebo (P < 0.05)	-0.3 kg with vildagliptin 50 mg qd, +1.3 kg with vildagliptin 50 mg bid and -0.4 kg with placebo. (P < 0.05 for the difference between vildagliptin 50 mg bid vs. placebo)	+2.7 kg with vildagliptin 50 mg bid, +1.5 kg with vildagliptin 50 mg qd, and +1.4 kg with placebo. (P < 0.05 for difference between vildagliptin 50 mg bid and placebo)	+1.3 kg with vildagliptin vs. +0.6 kg with placebo. (No significant difference between the 2 groups)
Withdrawal rates due to adverse effects	2.4% in the combined vildagliptin group vs. 3.3% with placebo	2.4% with vildagliptin 50 mg qd, 3.0% with vildagliptin 50 mg bid, and 1.7% in the placebo group	3.2% with vildagliptin 50 mg bid, 4.8% with vildagliptin 50 mg qd, and 2.5% with placebo	6.3% with vildagliptin vs. 0.7% with placebo

*All trials are randomized, double-blind, placebo-controlled, and multicenter.



add-on therapy in patients with type 2 diabetes already receiving metformin,¹⁴ glimepiride,¹⁵ pioglitazone,¹⁶ and insulin¹⁷ (Table 2). When added to ongoing metformin or pioglitazone therapy, vildagliptin (50 mg bid or 100 mg qd) reduced HbA_{1c} values by approximately 0.7 to 1.0% relative to baseline.^{14,16} However, when added to ongoing glimepiride and insulin therapy, the corresponding reductions in HbA_{1c} values were more modest, 0.6% and 0.5%, respectively.^{15,17} A single tablet combination formed of metformin plus vildagliptin has been approved in Europe under the name Eucreas.¹⁸

Vildagliptin Compared with Existing Antidiabetic Oral Agents (Table 3)

Vildagliptin (50 mg bid) was compared with metformin (up to 1000 mg bid) in 780 drug-naïve patients. After 2 years, the average reductions in HbA_{1c} values from baseline were significantly greater with metformin compared with vildagliptin, 1.5% and 1.0%, respectively.¹⁹ In another trial of elderly patients, the decrease in HbA_{1c} values with vildagliptin (50 mg bid) was not significantly different from that achieved with metformin, 0.6% and 0.7% relative to baseline, respectively.²⁰ However, in the latter trial, metformin was given in less than maximal effective doses (maximum dose used was 1500 mg/d). Vildagliptin (50 mg bid) was less effective than rosiglitazone (4 mg bid), with mean reductions in HbA_{1c} values of 0.8% and 1.4%, respectively after 2 years relative to baseline values.²¹ When added to ongoing metformin therapy, vildagliptin (50 mg bid) had comparable efficacy to submaximal doses of pioglitazone (30 mg qd), with mean reduction in HbA_{1c} levels of 0.6% with both agents after 52 weeks.²² Similarly, when added to a background of treatment with metformin, vildagliptin (50 mg bid) had similar efficacy to submaximal doses of glimepiride (mean dose 4.5 mg/d), with mean HbA_{1c} reductions of 0.4% and 0.5%, respectively after 1 year.²³

Finally, both vildagliptin (50 mg bid) and acarbose (up to 100 mg tid) were equally effective in reducing mean HbA_{1c} values by approximately 1.4%.²⁴ In the previous trial, the greater than expected decrease in HbA_{1c} values obtained with either agent may be due in part to the effects of lifestyle changes because the majority of patients had type 2 diabetes of recent diagnosis.²⁴

Taken together, direct comparison trials suggest that vildagliptin is less effective than metformin and

rosiglitazone, and most likely less effective than glimepiride and pioglitazone since the latter 2 drugs are used in less than their maximal effective doses.

Vildagliptin Compared with Other Incretin-Based Agents

Studies designed to compare vildagliptin with GLP-1 analogs such as exenatide or liraglutide are lacking. Regarding direct comparison with other DPP-4 inhibitors, one small non-randomized trial showed that both vildagliptin (50 mg bid) and sitagliptin (Januvia) (100 mg qd) had similar effects on levels of HbA_{1c}, fasting and postprandial glucose after 3 months of therapy in patients already receiving metformin.²⁵ Yet, blood glucose fluctuations decreased more in the vildagliptin group.²⁵ Clearly, more comparison trials are needed to better define differences between various incretin-based agents.

Patterns of HbA_{1c} Reduction with Vildagliptin

Review of efficacy data of vildagliptin revealed the following findings. First, maximum reduction of HbA_{1c} values were attained after 12–16 weeks followed by a slight rebound or a plateau up to the end of follow-up (up to 2 years).^{12,21} Second, subgroup analysis showed that greater HbA_{1c} reduction is achieved with higher HbA_{1c} levels at baseline, and in patients with shorter duration of diabetes.^{20,24} In general, the previous characteristics are also shared by other treatment modalities of diabetes. However, one characteristic feature of vildagliptin may be its higher efficacy in the elderly population. Indeed, most,^{14,15,17,20} but not all²² trials, suggest that vildagliptin may be more effective in the subgroup of patients above 65 year-old compared with younger individuals. For instance, in one 24-week trial of patients with advanced type 2 diabetes, the addition of vildagliptin (50 mg bid) to ongoing insulin therapy modestly reduced HbA_{1c} values by 0.5% and 0.3% compared with baseline and placebo, respectively.¹⁷ Yet, this reduction in HbA_{1c} values was limited to the subgroup of patients older than 65 years.¹⁷

Safety of Vildagliptin

Adverse effects of vildagliptin

In clinical trials lasting up to 2 years, the use of vildagliptin was well tolerated. Withdrawal rates

Table 3. Overview of trials of comparison of vildagliptin with other oral agents.*

Comparator drug (reference)	Metformin ¹⁹	Metformin ²⁰	Glimepiride ²³	Rosiglitazone ²¹	Pioglitazone ²²	Acarbose ²⁴
Mean age (years)	53	71	57	54	56	52
Mean body mass index (kg/m ²)	32.4	29.5	32.5	32.5	32.1	**26
Mean duration of known diabetes (years)	1 year (median)	3	5.7	2.5	6.4	1.2 60% of patients were diagnosed <3 months
Mean follow-up (weeks)	104	24	52	104	52	24
Mean baseline HbA _{1c} (%)	8.7	7.8	7.3	8.7	8.4	8.6
Background diabetes therapy	Drug-naïve	Drug-naïve	Metformin (mean dose 1898 mg/d)	Drug-naïve	Metformin (mean dose 2020 mg/d)	Drug-naïve
Patient groups	Vildagliptin 50 mg bid (n = 524) vs. metformin up to 2000 mg/d (n = 254)	Vildagliptin 100 mg qd (n = 169) vs. metformin up to 1500 mg/d (n = 166)	Vildagliptin 50 mg bid (n = 1389) vs. glimepiride up to 6 mg/d (mean dose 4.5 mg/d) (n = 1383)	Vildagliptin 50 mg bid (n = 515) vs. rosiglitazone 4 mg bid (n = 267)	Vildagliptin 50 mg bid (n = 295) vs. pioglitazone 30 mg qd (n = 281)	Vildagliptin 50 mg bid (n = 441) vs. acarbose up to 100 mg tid
Mean HbA _{1c} reduction from baseline	1.0% with vildagliptin vs. 1.5% with metformin (between group difference P < 0.05)	0.64% with vildagliptin vs. 0.75% with metformin. Difference not significant	0.44% with vildagliptin vs. 0.53% with glimepiride. Difference not significant	0.82% with vildagliptin vs. 1.44% with rosiglitazone (between group difference P < 0.05)	0.6% in both groups	1.4% with vildagliptin vs. 1.3% with acarbose
Mean change in weight from baseline	+0.5 kg with vildagliptin vs. -2.5 kg with metformin	-0.45 kg with vildagliptin vs. -1.25 kg with metformin	-0.2 kg with vildagliptin vs. +1.56 kg with glimepiride (between group difference P < 0.05)	+4.7 kg with rosiglitazone vs. no change with vildagliptin	+2.6 kg with pioglitazone vs. +0.2 kg with vildagliptin (between group difference P < 0.05)	-0.4 kg with vildagliptin vs. -1.7 kg with acarbose (between group difference P < 0.05)
Withdrawal rates due to adverse effects	4.6% with vildagliptin vs. 7.5% with metformin	3.6% with vildagliptin vs. 7.8% with metformin	5% with vildagliptin vs. 8% with glimepiride	5.3% with vildagliptin vs. 4% with rosiglitazone	3% with vildagliptin vs. 3.2% with pioglitazone at 24 weeks***	2.5% with vildagliptin vs. 3.2% with acarbose

*All trials are randomized, double-blind, and multi-center.

**In this trial, 90% of patients were Asian, and this may explain the relatively low body mass index.

***Withdrawal rates were only reported in the 24-week core study.³⁴



due to adverse effects in patients randomized to vildagliptin were generally similar to placebo and comparator drugs, and may be even slightly better than metformin (see Tables 1–3). However, these rates were higher in the vildagliptin group than the placebo group (6.3% vs. 0.7%) when added to ongoing insulin therapy.¹⁷

Based on data gathered from 8 trials, a meta-analysis suggested that headache was reported in slightly higher proportions of patients receiving vildagliptin than comparator drugs or placebo with a risk ratio of approximately 1.5.²⁶ Another analysis of phase III trials suggested that the use of vildagliptin may be associated with increased risk of angioedema (odds ratio ~4.5) in patients taking angiotensin-converting inhibitors although the absolute risk was small.²⁷

Effect on hypoglycemia

The incidence and severity of hypoglycemia were generally not increased with vildagliptin. Moreover, when vildagliptin was added to ongoing insulin therapy, hypoglycemia was less frequent than with placebo (reported by 23% vs. 30% of patients) despite similar insulin doses in the 2 groups.¹⁷ The low propensity for hypoglycemia with the use of vildagliptin is consistent with the glucose-dependent actions of incretin hormones, i.e. stimulation of insulin secretion by GLP-1 does not occur in the setting of hypoglycemia.³ Moreover, recent clamp studies suggest that vildagliptin may stimulate glucagon secretion as blood glucose drops below the normal range suggesting that the drug may also have a protective effect against hypoglycemia.²⁸

However, one notable exception is that vildagliptin may increase the risk of hypoglycemia when used in conjunction with a SU. Thus, the proportion of patients who reported hypoglycemia with the combination of vildagliptin (50 mg bid) and glimepiride was 3.6%, as opposed to 0.6% of patients who received glimepiride and placebo.¹⁵ Interestingly, similar observations were recorded when another DPP-4 inhibitor, sitagliptin²⁹ and the GLP-1 analog exenatide (Byetta)³⁰ were used with a SU concomitantly. Therefore, it may be wise to start with smaller doses of SU when used in conjunction with incretin-based drugs such as vildagliptin. The European Union approved vildagliptin in a dose of 50 mg once a day, rather than 50 mg bid, when used in combination with a SU.³¹

In addition, the maximum effective doses of SUs may be less than the maximum doses recommended by the corresponding manufacturer.³²

Effect on body weight

Overall, the effect of vildagliptin on weight is minimal. However, when used as part of combination therapy, the effect of vildagliptin on weight may vary according to the concomitant agent used (see Tables 1 and 2). For example, the vildagliptin/metformin combination was associated with a slight average weight loss of approximately 1.2 kg,¹² whereas the vildagliptin/pioglitazone high-dose combination was associated with an average weight gain of ~2 kg¹³ (Table 1).

Effect on lipid parameters

When used as monotherapy or part of combination therapy, vildagliptin has minimal or neutral effects on plasma levels of lipoproteins and triglycerides with changes of less than 5% relative to baseline. In one trial, vildagliptin had more favorable effects on lipid parameters when compared with glimepiride.²³

Effect on liver function

Treatment with vildagliptin at a dose of 100 mg qd resulted in slightly higher frequency of elevated hepatic enzymes.³³ Such abnormalities were not observed when using vildagliptin in a dose of 50 mg qd or bid. Therefore, it may be safer to use the latter doses. In addition, the manufacturer recommends the measurement of liver enzymes at baseline then every 3 months during the first year of treatment with vildagliptin.³³

Place of Vildagliptin in Diabetes Therapy

The drug profile of vildagliptin includes several advantages and limitations that should be considered when selecting the most appropriate patients with whom to use this drug. These are summarized in Table 4. Based on the available data, the use of vildagliptin may be useful in the following settings:

1. As second agent in patients with type 2 diabetes uncontrolled with metformin who cannot take SU or insulin because of concerns about hypoglycemia and/or weight gain.
2. As monotherapy in patients with mild diabetes ($HbA_{1c} < 8.0\%$) who cannot tolerate metformin

**Table 4.** Advantages and limitations of vildagliptin.**Advantages**

1. *Low risk of hypoglycemia.
2. Neutral effect on body weight.
3. Can be used as monotherapy or in combination therapy due to its distinct mechanism of action.
4. Reassuring safety profile and sustained efficacy in studies lasting up to 2 years.
5. **Simplicity of use.
6. May be particularly effective in the elderly population (see text).

Limitations

1. Less effective than metformin and rosiglitazone, and possibly less effective than glimepiride and pioglitazone.
2. Lack of long-term efficacy and safety data beyond 2 years.
3. Insufficient data regarding its use in renal insufficiency.
4. Higher price than metformin and sulfonylureas.
5. ***Vildagliptin trials may be open for different bias e.g. using the comparator drugs in less than their maximal effective doses.

*Except when used with SU (see text).

**Vildagliptin can be administered as 100 mg tablet once daily or 50 mg bid with or without food.

***While vildagliptin trials are randomized and double-blinded (Tables 1–3), they are all sponsored by the manufacturer.

due to gastrointestinal side effects or SU due to hypoglycemia.

3. In the elderly population, particularly those prone for hypoglycemia.

Conclusion and Future Needs

Despite its limitations, vildagliptin represents a useful addition to the existing armamentarium of antidiabetic drugs. Although this new drug appears less efficacious than most pre-existing agents, its effects on non-glycemic factors such as body weight, risk of hypoglycemia, and profile of adverse effects are different. These factors must be considered in order to choose the best candidates for using this drug. Unfortunately, there is lack of safety data regarding the use of vildagliptin in patients with various degrees of renal insufficiency. The latter concern is one of the main reasons behind the delay in its approval by the FDA.³³ Meanwhile, the evaluation of vildagliptin will not be satisfactory until its efficacy and safety are carefully examined in long-term trials

lasting several years. These trials should include cardiovascular morbidity and mortality as major outcomes.

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Disclosures

The authors report no conflicts of interest.

References

1. Nathan DM, Buse JB, Davidson M, et al. Medical management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy. A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2009;32:193–203.
2. Evans JMM, Donnelly LA, Emslie-Smith AM, et al. Metformin and reduced risk of cancer in diabetic patients. *BMJ*. 2005;330:1304–5.
3. Mikhail N. Is exenatide a useful addition to diabetes therapy? *Endocrine Practice*. 2006;12:307–14.
4. Russell-Jones D, Vaag A, Schmitz O, et al. on behalf of the Liraglutide Effect and Action in Diabetes 5 (LEAD-5) met+SU Study Group. Liraglutide vs. insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomized controlled trial. *Diabetologia*. 2009;52:2046–55.
5. Mikhail N. Incretin mimetics and dipeptidyl peptidase inhibitors in clinical trials for the treatment of type 2 diabetes. *Expert Opin Investig Drugs*. 2008;17:845–53.
6. Vilsboll T, Agero H, Krarup T, Holst JJ. Similar elimination rates of glucagon-like peptide-1 in obese type 2 diabetic patients and healthy subjects. *J Clin Endocrinol Metab*. 2003;88:220–4.
7. Mikhail N. Combination therapy with DPP-4 inhibitors and pioglitazone in type 2 diabetes: theoretical consideration and therapeutic potential. *Vasc Health Risk Management*. 2008;4(6):1221–7.
8. He H, Tran P, Yin H, et al. Absorption, metabolism, and excretion of [¹⁴C]vildagliptin, a novel dipeptidyl peptidase 4 inhibitor, in humans. *Drug Metabolism Disposition*. 2009;37:536–44.
9. Sunkara G, Sabo R, Wang Y, et al. Dose proportionality and the effect of food on vildagliptin, a novel dipeptidyl peptidase IV inhibitor, in healthy volunteers. *J Clin Pharmacol*. 2007;47:1152–8.
10. Scherbaum WA, Schweizer A, Mari A, et al. Evidence that vildagliptin attenuates deterioration of glycaemic control during 2-year treatment of patients with type 2 diabetes and mild hyperglycemia. *Diabetes Obes Metab*. 2008;10:1114–24.
11. Pi-Sunyer FX, Schweizer A, Mills D, Dejager S. Efficacy and tolerability of vildagliptin monotherapy in drug-naïve patients with type 2 diabetes. *Diabetes Res Clin Pract*. 2007;76:132–8.
12. Bosi E, Dotta F, Goodman M. Vildagliptin plus metformin combination therapy provides superior glycaemic control to individual monotherapy in treatment-naïve patients with type 2 diabetes. *Diabetes Obes Metab*. 2009;11:506–15.
13. Rosenstock J, Baron MA, Camisasca RP, et al. Efficacy and tolerability of initial combination therapy with vildagliptin and pioglitazone compared with component monotherapy in patients with type 2 diabetes. *Diabetes Obes Metab*. 2007;9:175–85.
14. Goodman M, Thurston H, Penman J. Efficacy and tolerability of vildagliptin in patients with type 2 diabetes inadequately controlled on metformin monotherapy. *Horm Metab Res*. 2009;41:368–73.
15. Garber AJ, Foley JE, Banerji MA, et al. Effects of vildagliptin on glucose control in patients with type 2 diabetes inadequately controlled with a sulfonylurea. *Diabetes Obes Metab*. 2008;10:1047–56.



16. Garber AJ, Schweizer A, Baron A, et al. Vildagliptin in combination with pioglitazone improves glycaemic control in patients with type 2 diabetes failing thiazolidinedione monotherapy: a randomized, placebo-controlled study. *Diabetes, Obes Metab*. 2007;9:166–74.
17. Fonesca V, Dejager S, Albrecht D, et al. Addition of vildagliptin to insulin improves glycaemic control in type 2 diabetes. *Diabetologia*. 2007;50:1148–55.
18. Tahrani AA, Piya MK, Barnett A. Drug evaluation: vildagliptin-metformin single-tablet combination. *Adv Ther*. 2009;26:138–54.
19. Goke B, Hershon K, Kerr D, et al. Efficacy and safety of vildagliptin monotherapy during 2-year treatment of drug-naïve patients with type 2 diabetes: comparison with metformin. *Horm Metab Res*. 2008;40:892–5.
20. Schweizer A, Dejager S, Bosi E. Comparison of vildagliptin and metformin monotherapy in elderly patients with type 2 diabetes: a 24-week, double-blind, randomized trial. *Diabetes Obesity Metabolism*. 2009;11:804–12.
21. Rosenstock J, Niggli M, Maldonado-Lutomirsky M. Long-term 2-year safety and efficacy of vildagliptin compared with rosiglitazone in drug-naïve patients with type 2 diabetes. *Diabetes Obes Metab*. 2009;11:571–8.
22. Bolli G, Dotta F, Colin L, et al. Comparison of vildagliptin and pioglitazone in patients with type 2 diabetes inadequately controlled with metformin. *Diabetes Obesity Metabolism*. 2009;11:589–95.
23. Ferranini E, Fonesca V, Zinman B, et al. Fifty-two-week efficacy and safety of vildagliptin vs. glimepiride in patients with type 2 diabetes mellitus inadequately controlled on metformin monotherapy. *Diabetes Obesity Metabolism*. 2009;11:157–66.
24. Pan C, Yang W, Barona JP, et al. Comparison of vildagliptin and acarbose monotherapy in patients with type 2 diabetes: a 24-week, double-blind, randomized trial. *Diabet Med*. 2008;25:435–41.
25. Marfella R, Barbieri M, Grella R, et al. Effects of vildagliptin twice daily vs. sitagliptin once daily on 24-hour acute glucose fluctuations. *J Diabetes Complications*. In press 2009.
26. Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes. Systemic review and meta-analysis. *JAMA*. 2007;298:194–206.
27. Brown NJ, Byiers S, Carr D, et al. Dipeptidyl peptidase-IV inhibitor use associated with increased risk of ACE inhibitor-associated angioedema. *Hypertension*. 2009;54:516–23.
28. Ahren B, Schweizer A, Dejager S, et al. Vildagliptin enhances islet responsiveness to both hyper- and hypoglycemia in patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2009;94:1236–43.
29. Hermansen K, Kipnes M, Luo E, et al; for the Sitagliptin Study 035 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes inadequately controlled on glimepiride and metformin. *Diabetes Obesity and Metabolism*. 2007;9:733–45.
30. Buse JB, Henry RR, Han J, et al. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. *Diabetes Care*. 2004;27:2628–35.
31. Mathieu C, Degrande E. Vildagliptin: a new oral treatment for type 2 diabetes mellitus. *Vasc Health Risk Management*. 2008;4:1349–60.
32. Bell DS. Practical considerations and guidelines for dosing sulfonylureas as monotherapy or combination therapy. *Clinical Therapeutics*. 2004;26:1714–27.
33. Ahren B. Clinical results of treating type 2 diabetic patients with sitagliptin, vildagliptin or saxagliptin—diabetes control and potential side effects. *Best Practice and Research Clinical Endocrinology and Metabolism*. 2009;23:487–98.
34. Bolli G, Dotta F, Rochotte E, Cohen SE. Efficacy and safety of vildagliptin vs. pioglitazone when added to metformin: a 24-week, randomized, double-blind study. *Diabetes Obesity Metabolism*. 2008;10:82–90.