1. Introduction

Diabetes is a major cause of morbidity and mortality with 8.3% of the US population (25.8 million people) affected as of 2011 [1]. It is a major cause of heart disease and stroke and is the seventh leading cause of death in the United States, killing > 1.4 million people worldwide in 2011 [2]. Diabetes is the leading cause of kidney failure, non-traumatic lower-limb amputations and new cases of blindness among adults. The UK Prospective Diabetes Study was one of many early studies highlighting the efficacy of glycemic control in preventing diabetic microvascular disease [3]. Those subjects in the intensive glucose control group achieved a median HbA1c of 7.0% over 10 years compared to 7.9% in the standard control group (p < 0.001). With this tighter glycemic control, the intensive group experienced a 25% risk reduction (p = 0.0099) in microvascular end points, such as retinopathy. As such, the American Diabetes Association (ADA) recommends lowering the HbA1c to < 7% for most individuals [4].

In order to achieve this goal, we now have a wide range of anti-diabetic drugs. Several factors such as each agent’s efficacy, mechanism of action, contraindications, side effects, risk for hypoglycemia and weight gain, cost, route of administration and dosing schedule help medical providers to determine which agent to prescribe.
In 2012, the ADA and European Association for the Study of Diabetes (EASD) released a joint position statement to help guide anti-hyperglycemic therapy in type 2 diabetes mellitus (T2DM) [5]. Their recommendations include metformin as first-line therapy but if not tolerated or contraindicated, another agent such as a sulfonylurea, glinide, pioglitazone, dipeptidyl peptidase-4 (DPP-4) inhibitor, insulin or glucagon-like peptide 1 (GLP-1) receptor agonist can be tried. If glycemic control is not achieved with monotherapy, dual-combination therapy should then be instituted with a step-up to triple combination therapy or multiple daily doses of insulin if not achieved on dual therapy.

DPP-4 inhibitors and GLP-1 receptor agonists are two classes of anti-diabetic drugs that have recently been introduced and focus specifically on the incretin system. The incretin effect was first noted in the 1960s when a larger meal produced and focus specifically on the incretin system. The incretin system is a set of hormones released from the intestine that mimic or enhance incretin effects were sought. DPP-4 inhibitors increase concentrations of endogenous GLP-1 and GIP by blocking their very rapid intravascular degradation by the DPP-4 enzyme, whereas GLP-1 agonists are analogs of GLP-1 that are resistant to degradation by DPP-4.

Box 1. Drug summary.

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Vildagliptin</th>
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<tbody>
<tr>
<td>Phase</td>
<td>Launched</td>
</tr>
<tr>
<td>Indication</td>
<td>Anti-hyperglycemic agent in type 2 diabetes mellitus</td>
</tr>
<tr>
<td>Pharmacology</td>
<td>Dipeptidyl-peptidase-4 inhibitor</td>
</tr>
<tr>
<td>Root of administration</td>
<td>Oral</td>
</tr>
<tr>
<td>Pivotal trial(s)</td>
<td>(27,41,47,48,52,55)</td>
</tr>
</tbody>
</table>

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2. Overview of the market

Sitagliptin, saxagliptin, linagliptin and alogliptin are DPP-4 inhibitors approved for treatment of T2DM in the United States and many other countries. Whereas vildagliptin is available for use in several countries, including the EU, China and Japan, its registration is no longer active with the US Food and Drug Administration. The very first DPP-4 inhibitor to be approved in the United States was sitagliptin, in 2006. Although similar in many respects, including efficacy, safety profile and patient tolerance, each agent is distinctive in its metabolism, excretion and recommended dosage. DPP-4 inhibitors are generally administered orally once daily with the exception of vildagliptin which is dosed twice daily (b.i.d.). In certain situations, such as moderate or severe renal impairment, vildagliptin may be administered once daily. Most DPP-4 inhibitors are predominantly excreted via the kidney and, therefore, require dose adjustment in renal impairment. The exception is linagliptin in which the most important elimination pathway is the liver [16]. No dosage adjustment is recommended in the setting of liver dysfunction for DPP-4 inhibitors, with the exception of vildagliptin which is not recommended for use in hepatic impairment [17]. Rare cases of increased alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels to ≥ 3 × the upper limit of normal have been reported with vildagliptin at a dosage of 100 mg/day; however, these elevations were generally asymptomatic and non-progressive at dosages of 50 mg/day or b.i.d. [18-20]. Although pharmacokinetic studies have found no significant difference in exposure to vildagliptin in patients with mild, moderate or severe hepatic impairment, the manufacturer does not recommend use in hepatic impairment and recommends that liver function be monitored in patients receiving vildagliptin [17,21]. Saxagliptin is primarily metabolized by cytochrome P450 (CYP) 3A4/5 and is the sole DPP-4 inhibitor that is a substrate for the CYP enzymes [16]. Therefore, drug-drug interactions with other CYP3A4/5 inhibitors, such as ketoconazole, clarithromycin and atazanavir, are of most concern with saxagliptin for which a dose reduction to 2.5 mg/day rather than 5 mg/day is recommended when coadministered [22,23].

3. Introduction to the compound

Vildagliptin has been approved since 2007 for treatment of T2DM in numerous countries throughout Europe, Latin America and Asia (Box 1). The FDA issued an ‘Approvable letter’ in 2007 requesting additional safety and efficacy data in individuals with renal impairment, additional data on skin-related findings noted in primate studies, but not in human studies, and preclinical data on the major metabolite of vildagliptin. The trade name for vildagliptin is Galvus®. It can be used as monotherapy in the treatment of T2DM as well as in dual combination with metformin, thiazolidinedione or a sulfonylurea and has been more recently approved with insulin [17]. Vildagliptin can also be coadministered with metformin and a sulfonylurea as triple-combination therapy and is formulated in combination with metformin (Eucreas®). Each tablet contains 50 mg of vildagliptin. The usual recommended dose is 50 mg b.i.d. when used as monotherapy, in combination with metformin, a thiazolidinedione or insulin. However, when used in dual combination with a sulfonylurea, 50 mg/day was found to be as effective as...
Table 1. Select pharmacokinetic properties of vildagliptin [21,25,27,28,39,40].

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
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<tbody>
<tr>
<td>Oral bioavailability</td>
<td>85%</td>
</tr>
<tr>
<td>Plasma protein binding</td>
<td>9.3%</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>70.5 l</td>
</tr>
<tr>
<td>Metabolism</td>
<td>hydrolysis</td>
</tr>
<tr>
<td>Major metabolite</td>
<td>M20.7 (LAY151) (inactive)</td>
</tr>
<tr>
<td>Renal elimination</td>
<td>85% (22.6% unchanged)</td>
</tr>
<tr>
<td>Fecal elimination</td>
<td>15%</td>
</tr>
<tr>
<td>Elimination half-life after oral dose</td>
<td>~ 2 – 3 h (independent of dose)</td>
</tr>
<tr>
<td>Use in hepatic impairment</td>
<td>No</td>
</tr>
<tr>
<td>Use with renal impairment</td>
<td>Yes*</td>
</tr>
</tbody>
</table>

*Reduced dose in moderate or severe renal impairment.

100 mg/day, and, therefore, this dose is recommended to reduce hypoglycemia [17]. No dosage adjustment is required in patients with mild chronic kidney disease (glomerular filtration rate [GFR] ≥ 50 ml/min/1.73 m²), but in those with moderate or severe renal impairment, the recommended dose if 50 mg/day [17]. There is experience, though limited, in patients on hemodialysis, and therefore vildagliptin, like any other DPP-4 inhibitor, should be used with caution in these patients [24].

4. Chemistry

The chemical name for vildagliptin is (1-[(3-hydroxy-1-adamantyl) amino] acetyl]-2-cyano-(S)-pyrrolidine) [25]. The molecular formula is C₁₇H₂₅N₃O₂ and the molecular weight is 303 g [26].

5. Pharmacokinetics and metabolism

5.1 Absorption

Select pharmacokinetic properties of vildagliptin are summarized in Table 1. Vildagliptin is rapidly absorbed with an absolute oral bioavailability of at least 85% [25,27]. Peak plasma concentration after oral administration in the fasting state is observed at an average of 1.7 h (range, 0.5 – 2 h) (tₘₐₓ). The Cₘₐₓ of vildagliptin decreases by 19% when administered with a standard high-fat meal, whereas tₘₐₓ is delayed by a median of 2.5 h compared to 1.75 h in the fasted state [28]. Given the concentration of vildagliptin required to achieve > 90% DPP-4 inhibition (IC₅₀) is 15 ng/ml, with an observed Cₘₐₓ of 431 ng/ml in the fed state (~ > 30-fold), a 19% reduction in Cₘₐₓ with food intake is unlikely to be clinically significant and therefore vildagliptin can be taken without regard to food. Food also does not alter the overall exposure to vildagliptin AUC.

5.2 Distribution

Vildagliptin distributes equally between plasma and red blood cells independent of concentration between 10 and 10,000 ng/ml with a mean human blood:plasma ratio of 1.0 [25]. The plasma protein binding of vildagliptin is low at a mean of 9.3%.

5.3 Metabolism

The predominant metabolic pathway is hydrolysis at the cyano moiety to form the pharmacologically inactive carboxylic acid metabolite (M20.7/LAY151), accounting for ~ 55% of circulating drug-related material following an oral dose [25]. Other metabolites detected in plasma include M15.3 (carboxylic metabolite formed from hydrolysis of the amide bond) and M20.2 (glucuronic acid conjugate of vildagliptin), accounting for 8.1 and 9.3% of the total plasma exposure, respectively. CYP enzymes do not metabolize vildagliptin to any quantifiable extent nor does vildagliptin inhibit or induce these enzymes. DPP-4, on the other hand, does contribute to the metabolism of vildagliptin. After an intravenous dose of vildagliptin, the total amount of unchanged vildagliptin in urine and feces was higher in Fischer 344 DPP-4 (-) rats compared with DPP-4 (+) rats, whereas metabolite M20.7 (LAY151) was less in the DPP-4 (-) rats [29]. This study suggested that ~ 20% of the cyano group hydrolysis reaction may be attributable to the DPP-4 enzyme. M20.2, seems to be primarily catalyzed by uridine diphosphate glucuronosyltransferase (UGT) 2B7 with lesser contributions by UGT2B17 and UGT2B4 [25,29].

5.4 Elimination

Renal excretion is the primary elimination pathway for vildagliptin. After a single oral 100 mg dose of radiolabeled vildagliptin was administered to healthy male subjects, ~ 85% of the dose was excreted in the urine and 15% in the feces [25]. Excretion was rapid with > 90% excreted within the first 48 h. About 27% of the administered dose is excreted as unchanged drug in urine and feces with renal excretion of unchanged vildagliptin accounting for 23% of the dose. M20.7 (LAY151) was the major metabolite identified in urine and feces. After intravenous administration of vildagliptin, renal clearance (13 l/h) was found to be approximately one-third of the total systemic clearance (41 l/h) with the rest ascribed to hydrolysis metabolism [27]. The mean elimination half-life (t₁/₂) after oral and intravenous of vildagliptin is ~ 2.13 and 1.67 h, respectively.

5.5 Drug interactions

In general, vildagliptin appears to have no significant drug-drug interactions with a number of commonly coadministered medications when studied in healthy subjects and patients with T2DM. Pharmacokinetic studies have not demonstrated a necessary dose adjustment for vildagliptin and/or studied compounds in these investigations. In addition, significant CYP interaction is minimal. As vildagliptin was envisioned to be prescribed in combination with other anti-hyperglycemic agents, steady-state pharmacokinetic studies with metformin, glibenclamide and...
pioglitazone were investigated. Subjects with T2DM were randomized to receive vildagliptin 100 mg/day, metformin 1000 mg/day or vildagliptin 100 mg plus metformin 1000 mg/day in a three-treatment crossover study. After 5 days of treatment, AUC$_{0-24}$ of vildagliptin was unaffected by coadministration of metformin, but C$_{max}$ declined by 18%. A 15% increase in AUC$_{0-24}$ of metformin was demonstrated with no effect on C$_{max}$—Neither minor effect was considered clinically meaningful [30]. Bioequivalence of vildagliptin/metformin combination tablets in healthy subjects at doses of 50/500, 50/850, or 50/1000 mg compared to administration of the free combination of the individual drugs was demonstrated. AUC, C$_{max}$, t$_{1/2}$ and total clearance of the drug from plasma was similar in the combination tablet or individual free tablet administration [31]. Vildagliptin 100 mg b.i.d. alone or in combination with glibenclamide 10 mg/day or vildagliptin 100 mg/day alone or in combination with pioglitzone 45 mg/day were investigated in patients with T2DM. Coadministration of vildagliptin with glibenclamide or pioglitzone demonstrated a small but not clinically significant effect on AUC or C$_{max}$ and 90% CIs for the geometric mean ratios were within acceptable bioequivalence reference range (0.8 – 1.25) [32].

Interaction of vildagliptin (100 mg) with three commonly prescribed anti-hypertensive medications: amlopidine (5 mg), valsartan (320 mg) and ramipril (5 mg) did not demonstrate a significant pharmacokinetic effect on these drugs or vildagliptin. AUC, C$_{max}$, t$_{max}$, t$_{1/2}$ and apparent clearance were not statistically different between vildagliptin and any study group. There was also no demonstrable effect of vildagliptin and ramipril and its co-metabolites [33]. Although not associated with the pharmacokinetics of vildagliptin, vildagliptin use may be associated with an increased risk of angioedema in patients taking ACE inhibitors (odds ratio [OR] = 4.57; 95% CI: 1.57 – 13.28) [34]. The proposed mechanism is decreased degradation of substance P, implicated in the pathogenesis of angioedema. Although the absolute risk was small, this potential drug–drug interaction may be important.

No dose adjustment of vildagliptin, warfarin, digoxin or simvastatin appears necessary when coadministered, as the pharmacokinetics of the above drugs were not altered when administered with vildagliptin [35-37]. The study with digoxin suggests that there is no significant interaction of vildagliptin with P-glycoprotein [35]. The findings that the pharmacokinetics of simvastatin, its active metabolites and warfarin were unaltered suggested no significant interaction of vildagliptin with CYP34A or CYP2C9 enzymes [36,37].

5.6 Special populations

The pharmacokinetics of vildagliptin appears unchanged by gender, body mass index (BMI) or age [38]. Forty healthy subjects were administered a single dose of vildagliptin 100 mg. No significant difference in mean C$_{max}$ exposure, plasma or renal clearance was demonstrated between genders. The peak concentration and exposure to M20.7 (LAY151) was higher in females compared to males, but was not statistically significant. The pharmacokinetic profiles in subjects with a BMI $\leq$ 25 kg/m$^2$ were comparable to those with a BMI $\geq$ 25 kg/m$^2$ as were the pharmacokinetics of M20.7 (LAY151). An equal number of subjects 18 to 40 years of age (n = 20) were compared to subjects $\geq$ 70 years of age (n = 20). Peak plasma concentration and exposure of vildagliptin were higher (17 and 31%, respectively) in elderly subjects compared with younger subjects. Renal clearance was reduced by 32% compared to younger subjects and correlated with renal function (r = 0.56, p = 0.01) in the elderly group. The authors propose that the reduced renal clearance may only be responsible for some of the observed increase in vildagliptin exposure in elderly subjects and suggest that other factors such as the rate or capacity of vildagliptin hydrolysis may also play a role in this relationship. Peak concentration and exposure to M20.7 (LAY151) were higher in the elderly subjects compared to younger subjects and those subjects with the highest exposure had the lowest calculated creatinine clearance; however, the estimated half-life of M20.7 (LAY151) remained unchanged ($7 - 8$ h) irrespective of the increased exposure. This has limited clinical importance as M20.7 (LAY151) is a pharmacologically inactive metabolite and nontoxic. Based on this study, no dose adjustment is recommended based on gender, BMI or age. The increased vildagliptin exposure in elderly subjects was not considered to be clinically meaningful.

Vildagliptin and its metabolites are primarily excreted by the kidneys. In a study of 96 subjects with mild (creatinine clearance [CL$_{CR}$]: 50 – 80 ml/min), moderate (CL$_{CR}$ 30 – 50 ml/min) and severe (CL$_{CR}$ < 30 ml/min) renal impairment, subjects received vildagliptin 50 mg/day for 14 days [39]. When matched against controls for age, gender and BMI, the mean AUC of vildagliptin increased by 40% in subjects with mild renal impairment, 71% in subjects with moderate renal impairment and 100% in subjects with severe renal impairment, respectively. The C$_{max}$ of vildagliptin increased similarly in all groups, 32 – 37%. Consequently, the authors suggested that a dose reduction of vildagliptin to 50 mg/day is appropriate in patients with moderate and severe renal impairment. In a larger cohort of 515 patients with T2DM and moderate (GFR 30 – 50 ml/min/1.73 m$^2$) or severe (GFR < 30 ml/min/1.73 m$^2$) renal impairment, vildagliptin 50 mg/day or placebo was randomized to subjects over a 24-week study period [40]. Subjects were either untreated or continued on prior anti-hyperglycemic agents (including insulin) provided that the dosage of prior medications was stable for 4 weeks. At completion, vildagliptin 50 mg/day added-on to prior anti-hyperglycemic therapy in subjects with moderate-to-severe renal impairment was safe and tolerable, with no meaningful changes in renal function. After 24 weeks, the differences in HbA$_{1c}$ between the vildagliptin and placebo groups were -0.5 and -0.6% in the moderate and severe renal insufficiency groups, respectively (p < 0.001). In the moderate renal insufficiency group, hypoglycemia, defined as symptoms plus
self-monitored blood glucose < 3.1 mmol/l (55 mg/dl) occurred in 17.2% of those receiving vildagliptin versus 11.6% of those receiving placebo. The incidence of severe hypoglycemia requiring third-party assistance was 1.2% with vildagliptin versus 1.6% with placebo. In patients with severe renal insufficiency the incidence of hypoglycemia was 15.3% with vildagliptin and 12.4% with placebo, and the incidence of severe hypoglycemia was 1.6 and 2.1%, respectively. This larger clinical study confirmed the safety of reduced dosing recommendations of vildagliptin in patients with moderate-to-severe renal impairment.

Although vildagliptin and its metabolites are ultimately excreted by the kidney, vildagliptin undergoes some metabolism in the liver where hepatic microsomes hydrolyze vildagliptin to M20.7 (LAY151). The pharmacokinetics of vildagliptin were studied in subjects with mild, moderate or severe liver impairment (defined using Child-Pugh clinical assessment scoring) [21]. A single dose of vildagliptin 100 mg orally was administered and parameters of interest were measured up to 36 h post-dose. Compared with healthy subjects, exposure to vildagliptin was lower in participants with mild or moderate hepatic dysfunction (20 and 8%, respectively). However, the exposure of vildagliptin increased by 22% with severe liver impairment. This study concluded that no dose adjustment of vildagliptin is necessary in patients with hepatic dysfunction, given there was no significant difference in exposure to vildagliptin in patients with varying degrees of hepatic impairment. However, rare cases of hepatic dysfunction have been reported in patients taking a dosage of 100 mg/day and so the European Medicines Agency summary of product characteristics states that vildagliptin should not be used in patients with hepatic impairment [17]. In one such trial, 3 of 248 patients receiving vildagliptin 100 mg/day plus metformin experienced persistent increases in ALT or AST levels to ≥ 3× the upper limit of normal compared to zero of 122 patients receiving metformin alone [19]. However, a meta-analysis of 38 studies where vildagliptin 50 mg b.i.d. was given for 12 to 104 weeks showed that vildagliptin was not associated with an increased risk of hepatic adverse events [20].

6. Clinical efficacy

The clinical efficacy of vildagliptin has been extensively studied in various populations with T2DM and vildagliptin has been found to be efficacious as both monotherapy as well as in combination with other antidiabetic oral agents and insulin [41-46]. Some of these studies are briefly described below. Monotherapy trials proved the ability of vildagliptin to reduce HbA1c by ~ 1% from baseline with minimal hypoglycemia and without weight gain. Drug-naïve patients with T2DM (mean baseline HbA1c of 8.4%) randomized to either placebo, vildagliptin 50 mg/day, vildagliptin 50 mg b.i.d. or vildagliptin 100 mg/day, experienced decreases in HbA1c of 0.3, 0.8, 0.8 or 0.9%, respectively (p < 0.01 for all groups vs placebo) over a 24-week period without hypoglycemia or weight gain [41]. A 52-week comparison study between vildagliptin 50 mg b.i.d. and metformin 1000 mg b.i.d. demonstrated reductions in HbA1c from baseline (8.7%) of 1.0% (p < 0.001) and 1.4% (p < 0.001), respectively, and therefore noninferiority of vildagliptin to metformin was not established [47]. Clinically meaningful decreases in HbA1c from baseline were maintained with both vildagliptin and metformin during a 2-year extension trial with mean changes in HbA1c from baseline to week 104 of -1 and -1.5% for vildagliptin and metformin, respectively [48]. Gastrointestinal adverse events were more common in the metformin- than vildagliptin-treated groups. Vildagliptin 50 mg b.i.d. was found to be noninferior to rosiglitazone 8 mg/day over a 24-week trial with decreases in HbA1c from baseline (8.7%) of 1.1% (p < 0.001) and 1.3% (p < 0.001), respectively, with some weight benefit with vildagliptin (-1.9 kg relative to rosiglitazone, p < 0.001) [49].

Combination studies of vildagliptin added onto other anti-diabetic agents, including metformin, glimepiride, pioglitazone, long-acting, intermediate-acting or premixed insulin, demonstrate clinically relevant reductions in HbA1c, from baseline to study end point [45,46,50-53]. Treatment-naïve patients with T2DM randomized to vildagliptin 50 mg b.i.d. + metformin 1000 mg b.i.d., vildagliptin 50 mg b.i.d. + metformin 500 mg b.i.d., vildagliptin 50 mg b.i.d. or metformin 1000 mg b.i.d. experienced decreases in HbA1c from baseline (8.7%) over 24 weeks of 1.8, 1.6, 1.1 and 1.4%, respectively [45]. For those with baseline HbA1c ≥ 10%, greater HbA1c reductions of 3.2, 2.7, 1.5 and 2.6%, respectively, occurred. All treatment groups had a comparable incidence of adverse events with no hypoglycemia or weight gain in the combination-therapy groups.

In another study of subjects inadequately controlled on glimepiride, the addition of vildagliptin 50 mg/day or 50 mg b.i.d. versus placebo resulted in between-group differences in HbA1c (vildagliptin vs placebo) of -0.6 and -0.7%, respectively (p < 0.001 vs placebo for both) [46]. For those with baseline HbA1c > 9%, the between-group difference was -1.0 and -0.9% for 50 and 100 mg/day versus placebo, respectively. The incidence of hypoglycemic events, defined as symptoms consistent with hypoglycemia plus a self-monitored blood glucose < 3.1 mmol/l (55 mg/dl), was slightly higher in the group receiving vildagliptin 100 mg (3.6%) versus the group receiving vildagliptin 50 mg (1.2%) or placebo (0.6%).

The efficacy and safety of vildagliptin versus glimepiride as add-on therapy to metformin has also been studied [52]. Those inadequately controlled on metformin monotherapy (mean dose 1898 mg/day) were randomized to vildagliptin 50 mg b.i.d. or glimepiride (titrated up to 6 mg/day). The mean change in HbA1c from baseline (7.3%) over 52 weeks was -0.4% with vildagliptin and -0.5% with glimepiride demonstrating noninferiority of vildagliptin. In addition, a similar percentage of patients in each group achieved the HbA1c
target of < 7% (54.1% with vildagliptin vs 55.5% with glimepiride). Compared to treatment with vildagliptin, glimepiride resulted in a 10-fold increased risk of hypoglycemia, defined as symptoms suggestive of hypoglycemia plus a self-monitored glucose < 3.1 mmol/l (55 mg/dl) (p < 0.01). No episodes of severe hypoglycemia requiring the assistance of another party occurred in the vildagliptin group compared with 10 episodes with glimepiride (p < 0.01). In addition, there was a significant, 1.79 kg weight loss in those treated with vildagliptin versus glimepiride (p < 0.001).

Vildagliptin has also been studied specifically in the elderly population and found to be efficacious and safe [54,55]. Patients with T2DM aged ≥ 70 years randomized to vildagliptin or placebo and studied over 24 weeks had changes of HbA1c of -0.9% from baseline (7.9%) with vildagliptin compared with -0.3% with placebo (p < 0.001) [55]. The number of patients with one or more adverse events was similar between treatment groups (47.5% for vildagliptin vs 45.3% for placebo), and most of these events were mild or moderate and not related to the study drug. Hypoglycemia, defined as symptoms suggestive of hypoglycemia and self-monitored plasma glucose of < 3.1 mmol/l (55 mg/dl) occurred in three (2.2%) of patients in the vildagliptin group (all on concomitant sulfonylureas) and one (0.7%) of those in the placebo group. Another study examined patients ≥ 65 years with moderate and severe renal impairment who were randomized to vildagliptin or placebo [40]. The percentage experiencing hypoglycemic events was similar with both vildagliptin (11.5%) and placebo (11.8%) in the moderate renal impairment group as well as in the severe renal impairment group (15.5 vs 18.8%, respectively).

7. Safety and tolerability data in clinical trials

Vildagliptin has minimal, if any, clinically significant effects on cardiovascular parameters, including lipids, blood pressure, vital signs and ECG recordings. A summary of the clinical parameters of vildagliptin is contained in Table 1. In a 24-week trial, no significant effect of vildagliptin treatment at any dose on lipid parameters was observed when compared to placebo [56,57]. A meta-analysis examining the effect of multiple DPP-4 inhibitors on lipids found that those treated with vildagliptin had significantly lower mean total cholesterol (difference in means -0.42 [-0.59; -0.25] mmol/l, -16.2 [-22.8; -9.7] mg/dl; p < 0.001) [58]. The difference in triglycerides and HDL were variable among studies and small (i.e., < Δ 0.2 mmol/l) when studied. However in a small study, treatment with vildagliptin for 4 weeks improved post-prandial plasma triglycerides and apolipoprotein B-48 containing particle metabolism after a high fat meal in subjects with T2DM [59]. As a follow up to that study, vildagliptin for 4 weeks in a similar population of T2DM demonstrated a reduction in remnant-like particles and an increase in LDL size [60]. In a study of drug-naïve subjects with T2DM, hypertension was reported in 1.2 – 7.4% of those receiving vildagliptin, depending on the dose, versus 2.25% in those receiving placebo [56]. In two other studies there were modest reductions in both systolic (1.4 – 4.1 mmHg reduction vs 1.5 mmHg reduction with placebo) and diastolic blood pressures (2 mmHg reduction vs 0.3 mmHg with placebo) [41,57]. Authors do contend, however, that any improvement in lipids or hypertension may be the result of weight loss associated with vildagliptin therapy. When reviewed, Keating found that no clinically significant changes occurred in vital signs or ECG recordings in patients who received vildagliptin monotherapy or in combination with metformin, pioglitazone or glimepiride [61].

A dedicated study of vildagliptin with cardiovascular endpoints has not been completed. In meta-analysis across 25 studies, vildagliptin treatment was not associated with increased cardiovascular or cerebrovascular events relative to all comparators (OR = 0.84 – 0.88) [62]. No statistical difference was noted in cardiovascular end points when age, gender and high cardiovascular risk were analyzed. In a prospective study of 96 patients with T2DM and coronary artery disease, vildagliptin did not impair myocardial ischemic preconditioning significantly [63].

Hypoglycemia is a rare occurrence with vildagliptin use. In all trials described, the definition of hypoglycemia used was symptoms suggestive of hypoglycemia plus self-monitored blood glucose < 3.1 mmol/l (55 mg/dl). In a monotherapy trial of vildagliptin, in a drug-naïve population, hypoglycemia occurred in one patient (0.6%) receiving vildagliptin 100 mg/day, two patients (1.2%) receiving vildagliptin 50 mg/day and zero patients receiving vildagliptin 50 mg b.i.d. [41]. In a comparison trial of vildagliptin 50 mg b.i.d. versus metformin 1000 mg b.i.d., in a drug-naïve population, studied over 1 year, hypoglycemia was low in both groups: 0.6% with vildagliptin and 0.4% with metformin with no serious events requiring third-party assistance occurring [47]. Hypoglycemia added-on to metformin resulted in no hypoglycemic events in another trial studying combination use [45]. When added-on to metformin, there is a 10-fold lower incidence of hypoglycemia with the addition of vildagliptin compared with glimepiride [52]. In addition, no severe episodes of hypoglycemia occurred with the addition of vildagliptin compared with 10 episodes with glimepiride (p < 0.01). When added-on to stable insulin doses ≤ 1 unit/kg/day (long-acting, intermediate-acting or premixed), there was no statistically significant difference in rates of hypoglycemia between vildagliptin and placebo groups (8.4 vs 7.2%, respectively, p = 0.66) [51]. Similarly, with the addition of vildagliptin 50 mg b.i.d. to glimepiride (≥ 1 mg/day), the incidence of hypoglycemia was low at 2% (2/102) in the vildagliptin group compared to 1% (1/100) in the placebo group [64].

Modest changes in bodyweight have been observed in those taking vildagliptin. Changes in weight from baseline of -1.8 (p = 0.001), -0.3 (p = 0.474), -0.8 (p = 0.034) and -1.4 kg (p < 0.001) kg were seen with vildagliptin 50 mg/day, 50 mg b.i.d., 100 mg/day and placebo, respectively [41].
Vildagliptin, specifically, is efficacious both as monotherapy and combination therapy with minimal risk of hypoglycemia and weight gain. Monotherapy trials have demonstrated its efficacy in lowering HbA1c from baseline by 0.8 – 1.1% [41,47,48]. Vildagliptin has proven noninferior to rosiglitazone and glimepiride in HbA1c reduction with less gastrointestinal adverse events than metformin, a more weight-favorable profile than rosiglitazone, and less hypoglycemia than glimepiride [47-49,52]. On the other hand, greater decreases in weight are observed with metformin than vildagliptin [47]. Studies of its pharmacokinetics demonstrate that vildagliptin is rapidly absorbed, can be taken without regard to food, is mainly metabolized by hydrolysis and is primarily excreted as an inactive metabolite by the kidney. It is well tolerated in combination with a number of other common anti-diabetic medications.

The ADA and EASD suggest that DPP-4 inhibitor use be considered, along with other agents including a sulfonylurea, glinide, pioglitazone, insulin or GLP-1 receptor agonist, if metformin is not tolerated or contraindicated [5]. Metformin is considered first-line therapy because of extensive experience with its use, no weight gain or hypoglycemia and a likely cardiovascular benefit. Vildagliptin could be considered an advisable first-line therapy alternative given its proven efficacy, rare hypoglycemia, weight neutrality, low incidence of drug interactions, demonstrated safety in mild chronic kidney disease and in the elderly. Additionally, vildagliptin has no significant deleterious effect on lipids, blood pressure or cardiovascular parameters [41,47-49,52,56,57,62]. If the DPP-4 class is chosen for therapy, vildagliptin may be chosen over saxagliptin in a patient on multiple medications to avoid drug-drug interactions. Otherwise, its twice-a-day dosing (compared to once-a-day dosing of all other members of this class) may be a deterrent to some, given its similar efficacy to other DPP-4 inhibitors. In a patient with kidney disease, especially on hemodialysis, linagliptin, which is eliminated mainly through the biliary route, may be a better alternative until the safety of vildagliptin in this population is further examined.

More studies regarding its safety in moderate and severe chronic kidney disease as well as in those with liver disease are needed. In addition, more ‘head-to-head’ clinical trials may better differentiate vildagliptin’s use against other DPP-4 inhibitors [69]. Vildagliptin has been evaluated in fewer drug-drug interaction studies compared to saxagliptin and sitagliptin. Post-marketing reports and future studies may expand the drug interaction profile of vildagliptin. Data regarding the lipid and cardiovascular effects of all DPP-4 inhibitors, including vildagliptin, would also be desirable. Although the DDP-4 inhibitors as a class are associated with a decrease in total cholesterol and triglycerides, limited studies have reported convincing data to support the use of one DPP-4 inhibitor over another with respect to cholesterol management. This information and, more practically, practitioners’ experience and

### 8. Expert opinion

Vildagliptin is one of five DPP-4 inhibitors currently approved for the treatment of T2DM, although not in the United States. The decision of which DPP-4 inhibitor to use can be difficult as there is little difference in efficacy among the agents [67,68]. However, certain factors such as potential for drug-drug interactions (high with saxagliptin, low with vildagliptin), use in renal impairment (no adjustment necessary for linagliptin) and use in hepatic impairment (cannot use vildagliptin) can help narrow one’s options.

### Table 1. Clinical parameters of vildagliptin are shown [41,47-49,52,56,57,62].

<table>
<thead>
<tr>
<th>Clinical parameter</th>
<th>Effect of vildagliptin</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ HbA1c from baseline</td>
<td>0.8-1.1%</td>
</tr>
<tr>
<td>Incidence of hypoglycemia</td>
<td>Rare (0.6-1.2% as monotherapy)</td>
</tr>
<tr>
<td>Body weight</td>
<td>↔</td>
</tr>
<tr>
<td>Lipids</td>
<td>↔</td>
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<tr>
<td>Blood pressure</td>
<td>↔</td>
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<tr>
<td>Cardiovascular or cerebrovascular risk</td>
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</table>
familiarity, dosing schedule and patient or insurance formulary preference will ultimately help in establishing the future role for vildagliptin in the management of T2DM.

**Bibliography**

Papers of special note have been highlighted as either of interest (●) or of considerable interest (★★) to readers.


27. He YL, Sadler BM, Sabo R, et al. The absolute oral bioavailability and

**Declaration of interest**

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**The pharmacokinetics of vildagliptin were well characterized in this study.**


**This large trial highlighted the efficacy and safety of vildagliptin compared with placebo.**

42. Fonseca V, Baron M, Shao Q, Dejager S. Sustained efficacy and reduced hypoglycemia during one year of treatment with vildagliptin added to insulin in patients with type 2 diabetes mellitus. Horm Metab Res 2008;40:427-30


47. Schweizer A, Couturier A, Foley JE, Dejager S. Comparison between vildagliptin and metformin to sustain reductions in HbA1c over 1 year in drug-naive patients with type 2 diabetes. Diabet Med 2007;24:955-61

**This large trial highlighted the efficacy and safety of vildagliptin versus metformin over 1 year.**


**This large trial highlighted the efficacy and safety of vildagliptin versus glimepiride over 52 weeks.**

a randomized, placebo-controlled study. Diabetes Obes Metab 2007;9:166-74


* This trial highlighted the efficacy and safety of vildagliptin in the elderly population.


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