


## VILDAGLIPTIN IN THE TREATMENT OF TYPE 2 DIABETES MELLITUS

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### Abstract

*Novel therapeutic approaches are continuously being researched in type 2 diabetes. The incretin class of anti-diabetic agents, consisting of glucagon-like peptide-1 agonists and dipeptidyl peptidase-4 inhibitors, has already found an important place in the current guidelines. Vildagliptin is a potent dipeptidyl peptidase-4 inhibitor, with numerous trials in type 2 diabetes treatment, both in monotherapy and in combination therapy. This review focuses on vildagliptin pharmacological properties, clinical efficacy and safety, and pharmacoeconomic data.*

**key words:** *diabetes treatment, DPP-4 inhibitors, vildagliptin*

### Background and aims


Given the ever increasing prevalence of type 2 diabetes mellitus (T2DM), novel therapeutic approaches are continuously being researched and clinically tested.

One of the newer classes of antidiabetic agents that has rapidly gained wide acceptance and a definitive place in the diabetes treatment guidelines is the incretin class. The incretin effect, augmentation of insulin secretion of pancreatic  $\beta$ -cells by oral administration of glucose, as compared to intravenous administration, is the result of the release (from L and K cells present in the intestinal wall) of active peptides (incretins): glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), and has been

well described for many years [1]. The incretins also have effects at other sites, delaying gastric emptying and centrally inhibiting caloric intake, all of which are therapeutically useful in T2DM. All of these effects are deficient in T2DM patients, especially by decreased levels of endogenous GLP-1 [2].

Pharmacologic intervention to improve the incretin effect consists of two distinct types of drugs: injectable GLP-1 agonists/mimetics (that act on the GLP-1 receptors in target tissues) and oral dipeptidyl peptidase-4 (DPP-4) inhibitors (that increase endogenous GLP-1 disponibility by decreasing its DPP-4 enzyme mediated inactivation).

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Vildagliptin (Galvus<sup>®</sup>) is a DPP-4 inhibitor that has been extensively studied in T2DM patients and has already been introduced in clinical usage [3].

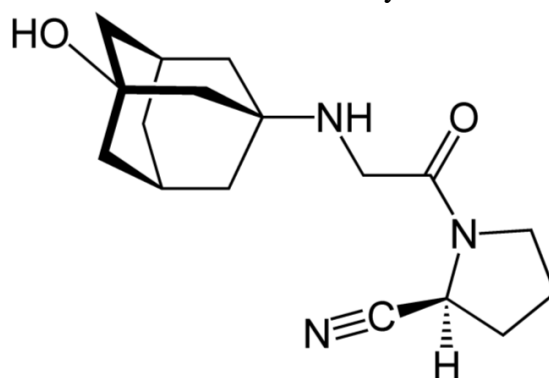
The aim of this review is to focus on vildagliptin pharmacologic characteristics, trials in T2DM patients and place in the current diabetes guidelines.

### Clinical pharmacology

In the following section relevant pharmacokinetic and pharmacodynamic properties of vildagliptin are presented.

**Pharmacokinetics:** Vildagliptin (Figure 1) is readily absorbed, with an absolute oral bioavailability of 85%. The maximum plasma concentration ( $C_{max}$ ) of  $245 \pm 65$  ng/ml is reached in 1,5 hours ( $t_{max}$ ) after a 50 mg dose. Concomitant administration of food increases  $t_{max}$ , reduces  $C_{max}$  and total vildagliptin exposure (area under curve - AUC), but this effect is of small clinical relevance (vildagliptin therefore can be administered with or without food) [3]. Both  $C_{max}$  and AUC are dose dependent over the dose range of 25-

200 mg. The drug is not highly bound to albumin, and distributes extensively into the extracellular space with a steady-state volume of distribution of 71 l following the intravenous administration of a 25 mg dose. The primary metabolic pathway for vildagliptin is hydrolysis at the cyano moiety (of which about 20% can be attributable to DPP-4 itself), and also at the amide bond. Glucuronidation by uridine diphosphate glucuronosyltransferase (UGT) 2B7 pathway has been also found. Oxidative catabolism via cytochrome P450 enzymes is very limited, with a very low potential for drug-to-drug interactions at this site. Renal clearance (as unchanged vildagliptin or metabolites) accounts for about 33% of total body clearance, the rest being primarily attributed to hydrolysis metabolism. The mean plasma elimination half-life ( $t_{1/2}$ ) is  $2,13 \pm 0,7$  hours after oral administration of a single or multiple doses (vildagliptin does not accumulate at steady-state). No significant difference in pharmacokinetics has been found between healthy volunteers and T2DM patients [4].



**Figure 1.** Vildagliptin ((S)-1-[N-(3-hydroxy-1-adamantyl)glycyl]pyrrolidine-2-carbonitrile) chemical formula (source: wikipedia.org).

**Drug-to-drug interactions:** Given the pharmacologic characteristics of vildagliptin the potential for clinically relevant drug-to-drug interactions appears to be low. Several

drug interaction studies have been carried out in healthy volunteers and T2DM patients to investigate potential interactions of vildagliptin with frequent co-medications.

Vildagliptin is mainly indicated in combination therapy with other anti-diabetic drugs. No pharmacokinetic interaction has been found between vildagliptin and metformin (1000 mg bid) [5], pioglitazone (45 mg qd) or glibenclamide (10 mg qd) [6] in studies in T2DM patients. Antihypertensive agents such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers or calcium channel blockers are commonly prescribed medications in diabetic patients. Interaction studies have been carried out for co-administration of vildagliptin with valsartan, ramipril and amlodipine with no relevant interaction found [7]. In addition, simvastatin, the cholesterol-lowering agent, did not interact with vildagliptin in a study on healthy subjects [8]. Drug-to drug interactions are especially important for drugs with narrow therapeutic indices: digoxin [9] and warfarine [10] have been studied in co-administration with vildagliptin, and no dose adjustment or additional monitoring seems warranted.

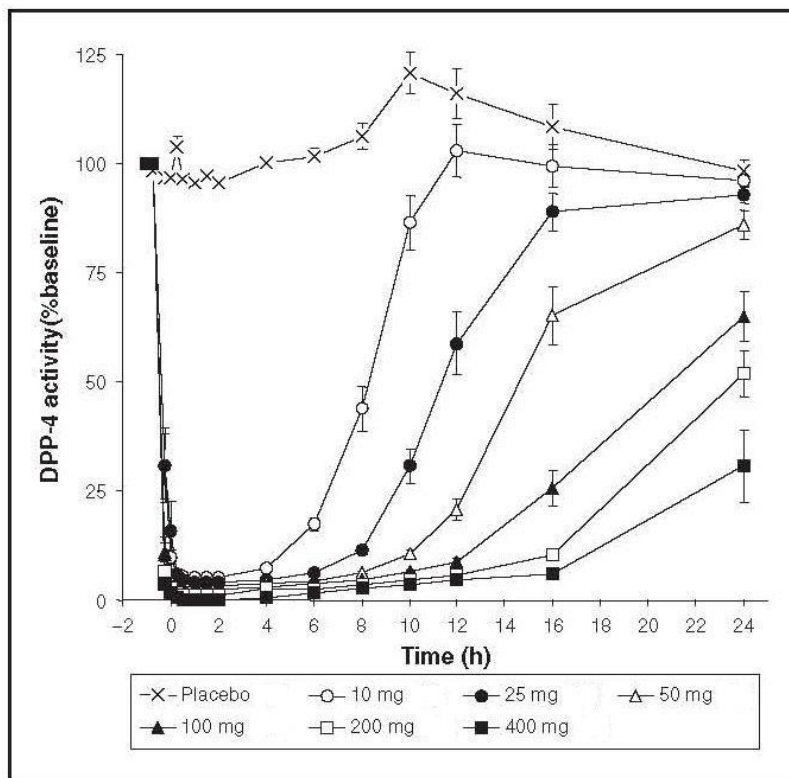
*Special patient populations:* Vildagliptin can be used without dose adjustment irrespective of age, gender and patient body mass index (BMI), with similar pharmacokinetics. Renal impairment does not alter the  $t_{1/2}$  of vildagliptin, but  $C_{max}$  and AUC of the primary hydrolysis metabolite have been found to increase in parallel with renal function (glomerular filtration rate - GFR). Moderate and severe renal impairment should prompt reduction of vildagliptin dose by half. The liver is one of the major sites for vildagliptin catabolism, but no correlation has been found between liver impairment and vildagliptin pharmacokinetics [4].

*Pharmacodynamics:* Endogenous or exogenous GLP-1 is rapidly degraded by the

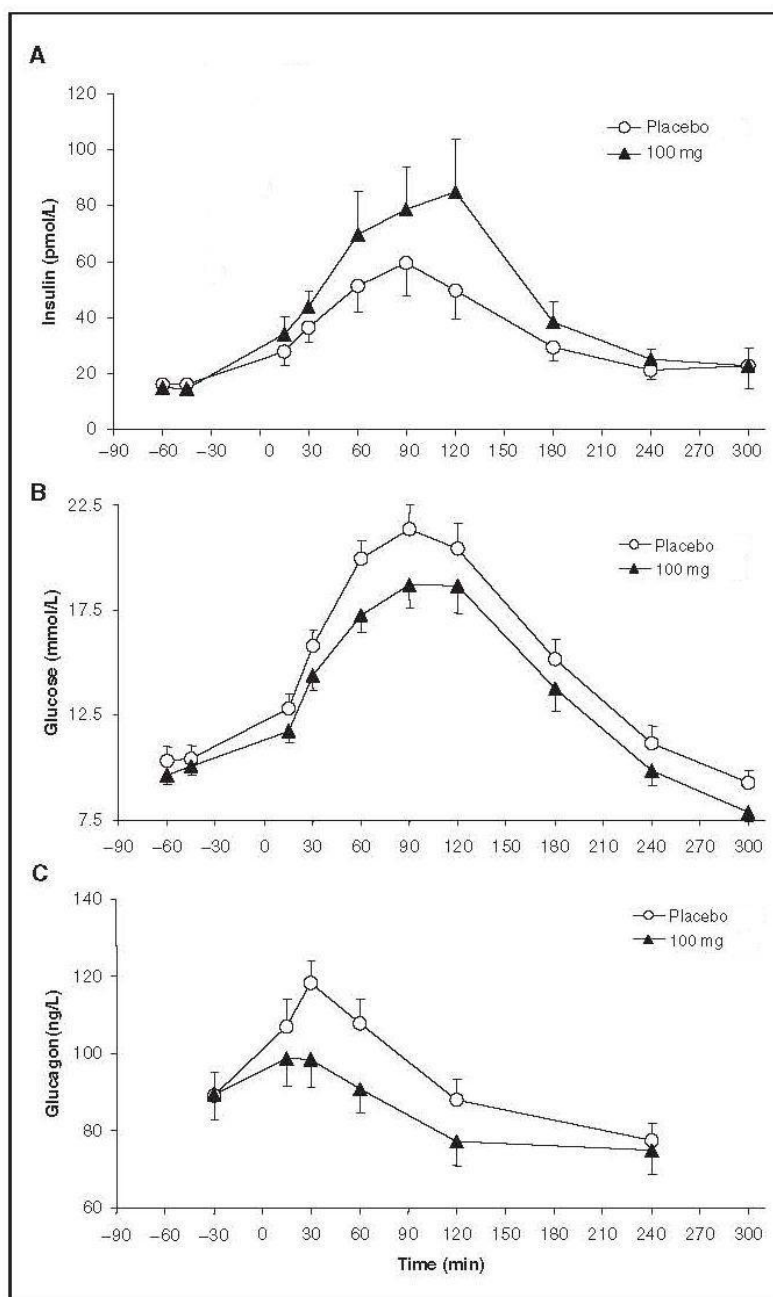
DPP-4 enzyme. GLP-1 therapeutic effects can be attained in T2DM patients only by continuous infusion. The observation that inhibiting DPP-4 action augments GLP-1 levels and effects opened the possibility for a new class of anti-diabetic drugs. Vildagliptin is a potent DPP-4 inhibitor, with a concentration required to achieve 50% DPP-4 inhibition ( $IC_{50}$ ) of 2,7 nmol/l in human plasma in vitro, and 4,5 nmol/l in healthy subjects and T2DM patients in vivo [4]. It is highly selective for DPP-4, having minimal or no activity on other dipeptidyl peptidases [11]. The high potency of vildagliptin is explained by its unique binding characteristics at the enzyme level. Vildagliptin has a long dissociation half-life (1 hour) from DPP-4, in contrast to other DPP-4 inhibitors, that are only competitive inhibitors. Given this characteristic, vildagliptin shows sustained therapeutic effect despite relatively short half-life [12]. A study carried out in T2DM patients assessed the dose-response relationships following single oral doses for a broad range of vildagliptin doses (10-400 mg). Time of onset and duration of effective DPP-4 inhibition were dose dependent, and reached a plateau at the 200 mg dose (Figure 2). Postprandial GLP-1 levels following 28-days of vildagliptin (25 mg or 100 mg bid) in T2DM patients increased 2-to-3-fold. Only the 100 mg dose increased fasting GLP-1 levels. Effects on GLP-1 concentration plateau at 100 mg, and are present even after a single dose. The effect of vildagliptin on glucose levels was investigated following multiple dosing regimens. Vildagliptin administration does not alter glucose concentration in healthy individuals, which is consistent with the glucose-dependent glucose-lowering action of

GLP-1. In T2DM patients subjected to standard mixed meals or an oral glucose tolerance test (OGTT), postprandial glucose excursions are significantly reduced (approximately 25-45 mg/dl) by vildagliptin at doses above 50 mg qd. Fasting blood glucose (FBG) was reduced by 20-30 mg/dl, only at doses above 50 mg bid. The insulin levels following a standard mixed meal in T2DM patients treated with vildagliptin versus placebo were not different, but, when concomitant glucose excursions were taken into account,  $\beta$ -cell response was shown to be significantly improved by vildagliptin. By contrast, following OGTT, which constitutes a stronger stimulus for insulin secretion, insulin levels were increased by approximately 35% [4,12]. The disposition index, a measure of insulin secretion corrected for the degree of

insulin sensitivity, was significantly increased (by 80%) in a study in patients treated for 12 weeks with vildagliptin 50 mg bid [13]. In T2DM patients, abnormalities in pancreatic  $\alpha$ -cells function bring about an inability of hyperglycemia to adequately suppress glucagon release. This is an important pathogenic component in T2DM, and a target for intervention. GLP-1 suppresses glucagon release from pancreatic  $\alpha$ -cells, in a glucose-dependent manner. Postprandial glucagon levels were significantly suppressed by vildagliptin, by approximately 15%. However, vildagliptin showed no effect on fasting glucagonemia [4,14]. The effects of vildagliptin on plasma insulin, glucose, and glucagon following an OGTT are shown in Figure 3.



**Figure 2.** Plasma DPP-4 activity expressed as a percentage of baseline (100% activity) following single oral doses of placebo or vildagliptin in patients with type 2 diabetes (adapted after He Y-L et al, [12]).



**Figure 3.** Plasma levels of (A) insulin, (B) glucose, and (C) glucagon during oral glucose tolerance tests performed 30 minutes after oral administration of placebo or vildagliptin (100 mg) (adapted after He Y-L et al, [12]).

### Clinical efficacy

A multitude of placebo-controlled trials have demonstrated the efficacy of vildagliptin for the treatment of T2DM, with respect to glycated hemoglobin A1c (HbA1c) and FBG reductions, both in monotherapy, but mostly in

combination therapy with other agents. Some of the results from such clinical trials are presented below.

*Monotherapy:* The efficacy of vildagliptin (50-100 mg/day) has been found to be lower than that of metformin (1500-2000 mg/day), in several direct comparisons. Metformin was

associated with slightly greater reductions in HbA1c and body weight, albeit with a greater incidence of gastrointestinal side-effects [15]. A 24-week randomized multiple-arm trial on 592 T2DM patients compared vildagliptin (100 mg qd) with pioglitazone (30 mg qd) in monotherapy (or two fixed combinations of the two agents). Overall results on HbA1c change and percent of patients achieving target HbA1c were similar between the vildagliptin and pioglitazone monotherapy arms [16]. One study reported comparative results of treatments with vildagliptin (50 mg bid) or acarbose (up-titrated to 100 mg tid). Decreases in HbA1c and FBG were similar between the two arms [17]. Overall, the reported reductions in HbA1c for monotherapy with vildagliptin in a recent review were 0,6-1,4% [15].

*Combination therapy:* Given the current guidelines for T2DM treatment the majority of trials with vildagliptin were performed in patients on different combination therapies. Addition of vildagliptin to metformin therapy in patients with inadequately controlled T2DM resulted in decreases of HbA1c and FBG of  $0,7\pm 0,1\%$  and  $14\pm 5$  mg/dl, and, respectively  $1,1\pm 0,1\%$  and  $30\pm 5$  mg/dl, for the 50 mg qd and 100 mg qd treatment arms in one trial, after 24 weeks [18]. In one analysis of 4 studies, efficacy of vildagliptin add-on to metformin was similar irrespective of T2DM duration, body mass index, insulin resistance and duration of metformin use [19]. Several comparisons were made between vildagliptin and a sulfonylurea as add-on to metformin. One of the longer trials randomized 3118 patients inadequately controlled on metformin to vildagliptin 50 mg bid and glimepiride (starting dose at 2 mg/day, up-titrated to a

maximum dose of 6 mg/day). After 2 years of treatment, adjusted mean change in HbA1c was similar between the two treatment arms, with similar proportions of patients reaching the target HbA1c <7%. Interestingly, treatment effect sustainability (defined as time from the initial response – lowest HbA1c in the first 6 months – until an increase of >0,3% in HbA1c) was statistically significant better on vildagliptin [20]. In addition, non-inferiority of vildagliptin (50 mg bid) over gliclazide (up to 320 mg/day) was established in a 52-week, randomized trial, with similar effects observed on HbA1c and FBG [21]. Comparisons to sulfonylureas showed a significantly lower incidence of hypoglycemia in vildagliptin treated patients, more of the patients being able to safely attain target HbA1c. In a 52-week, randomized trial vildagliptin treatment (50 mg bid) was compared with pioglitazone (30 mg qd) on top of metformin. Change in HbA1c ( $-0,6\%$ ) was similar between the treatment arms, with more serious adverse events and more weight gain in patients on the pioglitazone arm [22]. Addition of a DPP-4 inhibitor to insulin is an already established treatment strategy. One 24-weeks randomized trial compared vildagliptin (50 mg bid) to placebo as add-on to insulin therapy, with or without metformin. Difference in HbA1c versus placebo was  $-0,7\pm 0,1\%$  for vildagliptin, with no additional hypoglycemia and no weight gain [23].

*Head-to-head comparisons between DPP-4 inhibitors:* Within-class pharmacologic different characteristics raise the question of possible differences of efficacy and safety profiles between various DPP-4 inhibitors. Only scarce data is, however, available regarding direct comparisons. In the absence

of randomized trials directly comparing DPP-4 inhibitors, such information can only be found in meta-analyses. One meta-analysis of 12 trials with the DPP-4 inhibitor sitagliptin and 11 trials with vildagliptin, showed similar results of the two agents on HbA1c versus placebo (-0,79% vs. -0,67%) [24]. Another meta-analysis on Japanese T2DM patients showed a significantly greater reduction in HbA1c for vildagliptin treatment (50 mg bid) versus sitagliptin (0,28%, and 0,35% HbA1c difference for sitagliptin 50 mg qd, and 100 qd doses, respectively) [25]. A comprehensive meta-analysis published in 2012, comparing effects throughout the incretin class, showed similar reductions in HbA1c, FBG and trends toward weight loss on DPP-4 inhibitors alogliptin, linagliptin, saxagliptin and sitagliptin, and a greater reduction of HbA1c and FBG on vildagliptin treatment, but with marked variability introduced primarily by a single trial [26]. In conclusion, some evidence points to a greater effect of vildagliptin as compared to other DPP-4 inhibitors, but proper head-to-head trials may be warranted to clarify this issue. Two studies compared continuous glucose profiles with vildagliptin versus sitagliptin as add-on to metformin, looking at 24-hour glycemic variability. Vildagliptin was associated in both these studies with significant decreases in mean amplitude of glycemic excursions [27,28].

*Non-glycemic therapeutic effects:* Body weight changes during anti-diabetic therapy are an important clinical outcome. Therapy with DPP-4 inhibitors is in general weight neutral, or associated with a trend towards weight loss [26]. Modest body weight loss was observed on the vildagliptin arms as add-on to metformin. When compared to sulfonylureas,

vildagliptin has shown a significant weight advantage, for similar HbA1c reductions (patients randomized on sulfonylurea therapy experienced more weight gain) [15]. Lipid profile changes were observed in many studies involving incretin therapy. In one trial, treatment with vildagliptin for 4 weeks was associated with improvements in postprandial plasma triglycerides (and apo-B48) after a fat-rich meal [29]. Slight reductions in mean systolic and diastolic blood pressures were also seen with vildagliptin treatment versus placebo in two trials [18,30].

### **Clinical safety and tolerability**

As a therapeutic class, the DPP-4 inhibitors have an excellent safety profile. In many trials adverse events incidence was no different from placebo. Also, two meta-analyses have been conducted exploring adverse events with vildagliptin versus comparators, and also the cardiovascular safety of vildagliptin. Data from these researches will be presented below.

*General tolerability profile:* Oral vildagliptin, when used in approved doses, is generally well tolerated. The most commonly reported adverse events in clinical trials, versus placebo, were: upper respiratory tract infections (including nasopharyngitis, bronchitis), back and joint pain, headache, and dizziness. These occurred in >5% of treated patients, and were generally low or moderate in intensity. Gastrointestinal disturbances (nausea, diarrhea, dyspepsia, flatulence) were no different from placebo treatment. In head-to-head trials against metformin, gastrointestinal side effects were significantly more frequent on metformin treatment [31]. One post-marketing observational study on

3834 patients treated with vildagliptin and metformin (add-on or fixed combination), or other oral anti-diabetics, confirmed the good tolerability of vildagliptin [32]. Given that the DPP-4 enzyme (designated CD226) is also located on immune cells, concerns regarding immune function suppression have been raised (and fueled by the slightly increased risk of upper respiratory tract infections seen with DPP-4 inhibitors). Also, in pre-clinical trials on monkeys, cutaneous lesions associated with vildagliptin have been documented [3]. However, in a report on pooled data from 38 studies with vildagliptin (>7000 subject-years of exposure), this treatment was not associated with an increased risk for immune system suppression (infection or infestation related adverse events) or skin related adverse events [33].

*Hepatic safety:* In the same report mentioned above [33], vildagliptin treatment was not associated with drug-induced liver injury. Although some cases with elevation of aspartate transaminase (AST)/alanine transaminase (ALT)>3 times the upper limit of normal (ULN) did occur on vildagliptin treatment, important (>10-20 x ULN) increases in ALT/AST, with or without increases in bilirubin >2 x ULN, were exceedingly rare, and no different from comparators. No increased risk for hepatic adverse events was found on vildagliptin [33]. According to the current summary of product characteristics, liver tests should be obtained before initiation of vildagliptin and periodically after. Persistent elevations of ALT/AST>3 x ULN, jaundice or hepatic failure should prompt cessation of vildagliptin administration [3].

*Pancreatitis:* Several cases of suspected vildagliptin drug-related acute pancreatitis

have been reported post-marketing. In the report mentioned above [33], no evidence has been found for an increased risk of pancreatitis-related adverse events with vildagliptin [33]. Nevertheless, patients on this treatment should be informed about symptoms suggestive of pancreatitis (mainly severe abdominal pain) [3].

*Renal safety:* The presence of mild renal impairment (GFR>50 ml/min and <80 ml/min) does not affect the safety of vildagliptin [33]. One trial explored the renal safety of vildagliptin 50 mg qd in patients with moderate (GFR=30-50 ml/min) and severe (GFR<30 ml/min) renal impairment. No difference in the adverse and severe adverse events profile, as well as adverse events leading to discontinuation of treatment, was found between vildagliptin and placebo (the background treatment consisted mostly of insulin) [34]. Based on the drug pharmacokinetic properties, dosage should be reduced to 50 mg qd, when used in patients with moderate and severe renal impairment. Vildagliptin should not be administered to T2DM patients on renal replacement therapy, due to lack of experience in this subgroup [3].

*Cardiovascular safety:* One comprehensive analysis on data pooled from 25 phase III studies of vildagliptin (50 mg qd or 50 mg bid) assessed the incidence of major cardiovascular end-points, against all comparators (placebo or active). The composite end-point of acute coronary syndrome, transient ischemic attack, stroke and cardiovascular death, was adjudicated by an independent committee. Relative to all comparators, vildagliptin was associated with a relative risk of <1 (95% CI 0,37-2,11, and 0,62-1,14, for the 50 mg/day, and 100 mg/day

doses, respectively) for adjudication of the composite end-point. The result was consistent across all subgroups, defined by age, gender and cardiovascular risk status [35]. Vildagliptin should not be administered to patients with heart failure in New York Heart Association functional classes III and IV, due to lack of experience from clinical trials [3]. Overall, based on all the data available, no cardiovascular safety concern has been raised regarding vildagliptin treatment.

### **Pharmacoeconomics of vildagliptin treatment**

Type 2 diabetes is associated with important direct and indirect costs. Limiting these costs is one of the objectives of healthcare systems worldwide. Because the newer agents introduced in clinical use are somewhat expensive, intense scrutiny was carried out in respect to their cost-effectiveness.

One observational study on 1046 patients with secondary failure of metformin treatment that were initiated on fixed-dose combination vildagliptin/metformin showed a reduction of annual indirect costs of €400 per working patient and €135 per patient in general (through reduction of activity impairment and absenteeism from work). Mean healthcare costs per patient diminished by 19,2% in the second semester of treatment. Also, patient satisfaction evaluated by questionnaires was increased [36]. An analysis carried out in 2010 in Great Britain by the Guideline Development Group, for the purpose of updating the 2008 National Institute of Health and Clinical Excellence (NICE) Guidelines, looked at the cost-effectiveness profile of newer agents (including, but not only limited to, exenatide, sitagliptin and vildagliptin).

Cost and quality-of-life estimates were first evaluated for a representative male patient with a BMI of 30 kg/m<sup>2</sup>, who was assumed to be reaching the 7,5% HbA1c intensification threshold. In the United Kingdom (UK), the total annual costs of treatment with DPP-4 inhibitors were between £386 and £460, lower than those for exenatide, glitazones, or basal insulins (glargine or detemir). Vildagliptin was considered clinically equivalent to pioglitazone in terms of potency, but with the associated benefit of avoiding weight gain, and associated costs of around £600 lower (in the UK). Taking into account HbA1c lowering efficacy (0,6-0,7% versus placebo), weight effects and the low hypoglycemia risk profile, the report concluded that the DPP-4 inhibitors are cost-effective agents [37].

### **Clinical use according to current guidelines**

Numerous trials in T2DM patients have shown that improving and maintaining glycemic control reduces long-term complications. The current guidelines recommend starting metformin together with optimization of lifestyle at the diagnosis of T2DM [38]. However, some patients do not tolerate metformin treatment (because of gastrointestinal side-effects), and most of the patients will eventually require combination therapy in order to reach the HbA1c goals, given the progressive nature of the disease.

The incretin class of anti-diabetic agents has rapidly found a place in the current consensus guidelines. Vildagliptin is approved for use in T2DM patients. In most of the trials with vildagliptin, the HbA1c lowering effect is achieved in the first 12 weeks of treatment. Higher HbA1c values at baseline were associated with a higher lowering effect of

vildagliptin treatment [31]. It is to be noted that baseline HbA1c is a valuable parameter when selecting the treatment intensification option. High baseline HbA1c values generally recommend agents that have proven to be more potent (including insulin), but at the same time lower HbA1c values should prompt consideration for treatment with anti-diabetics with a favorable hypoglycemia risk profile.

The DPP-4 inhibitors mechanism of action offers certain advantages in terms of their use in combination therapy. The glucose-dependent action of vildagliptin recommends its usage on top of metformin, instead of sulfonylureas or insulin, when hypoglycemia concerns exist. When compared to GLP-1 agonists, DPP-4 inhibitors in general have lower potency and a lower or no weight effect, but have a better tolerability profile. The weight neutrality recommends vildagliptin when compared to glitazones in patients with weight problems. Also, vildagliptin can be a useful agent as add-on to basal insulin therapy, as a safe and effective means of controlling postprandial hyperglycemia.

Vildagliptin is a safe agent, which can be used in older, high-cardiovascular risk, and

renal impaired patients. No specific safety concerns, cardiovascular or other, have been raised for vildagliptin in the post-marketing period.

Currently, vildagliptin is indicated as monotherapy in T2DM patients that cannot receive metformin, in combination therapy with metformin, a sulfonylurea or a glitazone, in triple oral therapy with metformin and a sulfonylurea, and finally, in association with insulin (with or without metformin) [3]. Vildagliptin is also available in 50/850 mg and 50/1000 mg fixed-dose combinations with metformin (Eucreas<sup>®</sup>).

### Conclusions

Vildagliptin is an orally administered potent DPP-4 inhibitor that improves HbA1c and FBG with no weight gain and a very low risk for hypoglycemia. Vildagliptin is approved for use in T2DM patients in multiple combinations or in monotherapy. Existing pharmacoeconomic analyses suggest its cost-effectiveness.

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