ROLE OF VILDAGLIPTIN- Dipeptidyl peptidase-4 inhibitor in patients with Type 2 diabetes mellitus - an overview

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ABSTRACT

Diabetes is a condition in which the body does not produce or respond to insulin, a hormone that regulates the level of sugar in the blood. It is characterized by abnormally high levels of glucose in the blood. They are classified into three categories Type 1 Diabetes mellitus (DM), Type 2 Diabetes mellitus (DM) and Gestational diabetes. The prevalence of T2DM is increasing rapidly and plays a vital role in the genesis of the pathophysiological events. Oral hypoglycemic agents are used in the treatment of T2DM and they have their own limitations.

Newer drugs have been invented for the treatment of T2DM. Dipeptidyl peptidase 4 (DPP-4) inhibitors play an important role in the treatment of T2DM. There are six DPP-4 inhibitor identified (Sitagliptin, Vildagliptin, Saxagliptin, Alogliptin, Linagliptin and teneligliptin). Vildagliptin is a second DPP-4 inhibitor approved by US FDA in February 2007. It is an orally active, potent, and selective DPP-4 inhibitor shown to be effective and well tolerated by patients with T2DM. It is rapidly and well absorbed with an oral bioavailability of 85%. It is effective either as monotherapy or in combination with other antidiabetic agents. It has got lower incidence of hypoglycemic symptoms when used as a monotherapy or combination therapy with other oral hypoglycemic drugs. Vildagliptin once daily or twice daily is found to
be an effective, safety and well tolerated DPP-4 inhibitor as monotherapy or combination therapy with oral hypoglycemic agents (OHA) or insulin in the treatment of T2DM patients.

KEYWORDS: Vildagliptin, diabetes mellitus, therapeutic management.

INTRODUCTION

Diabetes mellitus (DM), commonly referred to as diabetes, is a group of metabolic diseases characterized by high blood sugar levels over a prolonged period. Symptoms of high blood sugar include frequent urination, increased thirst, and increased hunger. If left untreated, diabetes can cause many complications. Acute complications include diabetic ketoacidosis and nonketotic hyperosmolar coma. Serious long-term complications include cardiovascular disease, stroke, chronic kidney failure, foot ulcers, and damage to the eyes. Diabetes is due to either the pancreas not producing enough insulin or the cells of the body not responding properly to the insulin produced. There are three main types of diabetes mellitus: Type 1 DM results from the pancreas failure to produce enough insulin. This is also called "Insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes". The cause is unknown. Type 2 DM begins with insulin resistance, a condition in which cells fail to respond to insulin properly. As the disease progresses a lack of insulin may also develop. This is also known as "Non insulin-dependent diabetes mellitus" (NIDDM) or "adult-onset diabetes". The primary cause is excessive body weight and not enough exercise. Gestational diabetes, is the third main form and occurs when pregnant women without a previous history of diabetes develop a high blood sugar level.\(^{[1]}\)

T2DM is a chronic disease and is characterized by high levels of glucose in the blood. T2DM is also called adult-onset diabetes, accounting for about 90% to 95% of all diagnosed cases of diabetes. The prevalence of Type 2 Diabetes Mellitus (DM) is increasing all over the world, especially in South Asia. India has largest population of diabetic patients. The International Diabetes Federation (IDF) estimates the number of people with diabetes in India will reach 80 million by the year 2025.\(^{[2]}\)

There are at least seven different classes of agents used as monotherapy or in combinations for the treatment of diabetes mellitus. These include metformin, sulphonylureas, meglinitides, alpha-glucosidase inhibitors, thiazolidinediones (TZD), glucagon like peptide-1 (GLP-1) agonists and insulin. Many conventional agents frequently exhibit reduced efficacy over time, leading to inadequate glycemic control. Several of these agents are also associated with
adverse effects that include weight gain, hypoglycemia and gastrointestinal distress. There is a need therefore, for alternative therapies that can overcome the limitations associated with conventional anti-hyperglycemic medications.\[2\]

Dipeptidyl peptidase 4 (DPP-4) inhibitors represent a new therapeutic approach in the treatment of T2 DM patient. At present 6 DPP-4 inhibitors are available in the Market - Sitagliptin, Vildagliptin, Saxagliptin, Alogliptin, Linagliptin and teneligliptin.\[3\] DPP-4 act by enhancing the level of active incretin hormones. Incretin hormones such as glucagon like peptide-I (GLP-1) and the glucose dependent insulinoitropic polypeptide (GIP) are released from the intestine cell following meal ingestion. The GLP-I and GIP stimulate insulin secretion from pancreatic-β cell and the GLP –I inhibit glucagon secretion from pancreatic α-cells which reduces the plasma glucose levels. Glitpns show significant improvements in glycemic control and are well tolerated, particularly with regard to weight change and hypoglycemia. Hence, gliptins are considered as useful agents for the treatment of type 2 diabetes mellitus.\[4\]

Sitagliptin was the first of the DPP-4i to be approved by the US Food and Drug Administration in 2006. This was followed by the approval of vildagliptin in February 2007. Recently, saxaglipitin in 2009 and alogliptin in 2010 (presently only in Japan) are available in the pharmaceutical market. Compounds such as sitagliptin (β-amino acid based) and vildagliptin which are nitrile containing inhibitors.\[5\]

**VILDAGLIPTIN**

Vildagliptin is the second DPP-4 inhibitor approved for human use and is indicated for the control of hyperglycemia in patients with type 2 DM. Vildagliptin produces sustained inhibition of DPP-4 when administered and produces moderate increases in GLP-1 and GIP. Vildagliptin is available as 50mg and 100mg tablets with a recommended dose of 50mg once daily if used in combination with metformin or a TZD and 50mg once daily if used in combination with a sulfonylurea. The chemical formula of Vildagliptin is depicted in Fig.1.

![Figure 1: Chemical structure of Vildagliptin ((S)-1-[N-(3-hydroxy-1-adamantyl) glycyl] pyrrolidine-2-carbonitrile)
Absorption
The DPP-4i are all orally available and are rapidly absorbed, with significant inhibition of plasma DPP-4 activity being seen within 5 min of administration. Vildagliptin is absorbed rapidly and has got oral bioavailability of 85\%\textsuperscript{[6]}

Distribution
The available data indicates that the volume of distribution of the various inhibitors in humans is greater than the total body water. Vildagliptin is well distributed into the extra vascular spaces and the volume of distribution is about 70L which is more than the total body water\textsuperscript{[6,7]}. There is some indirect evidence that Vildagliptin may be able to cross the cell membrane. Vildagliptin minimally binds to the plasma protein (10\%).\textsuperscript{[8,7]} Vildagliptin are found in fewer amounts in the brain which indicates that it may not cross the blood brain barrier. It crosses the placenta freely (EMEA)\textsuperscript{[7]}

Metabolism
The major metabolic pathway for vildagliptin is hydrolysis at its cyano moiety, which occurs in the liver and other tissues via a CYP450-independent mechanism, to produce a carboxylic acid metabolite (M20.7/LAY151) and four minor metabolites\textsuperscript{[8,7]}

Excretion
The elimination and excretion is mainly through renal route about 22\% of the dose remains unchanged in the urine and 50\% appearing as the major metabolite (M20.7); active transport in addition to glomerular filtration was indicated to be involved in the elimination of Vildagliptin\textsuperscript{[8]}

Pharmacodynamic
It is highly selective for DPP-4, having minimal or no activity on other dipeptidyl peptidases\textsuperscript{[11]} Vildagliptin has a long dissociation half-life (1 hour) from DPP-4, in contrast to other DPP-4 inhibitors, that are only competitive inhibitors. In T2DM patients subjected to standard mixed meals or an oral glucose tolerance test (OGTT), postprandial glucose excursions are significantly reduced (approximately 25-45mg/dl) by Vildagliptin at doses above 50mg qd. Fasting blood glucose (FBG) was reduced by 20-30mg/dl, only at doses above 50mg 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, β-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%.

**Inhibitory effect**

Inhibition of DPP-4 by vildagliptin has been described as a two-step process that involves the formation of a reversible covalent enzyme inhibitor complex in which there is a slow rate of inhibitor binding and a slow rate of inhibitor dissociation, resulting in the enzyme slowly equilibrating between the active and inactive forms. This means that the catalytic activity will be inhibited even after the free drug has been cleared from the circulation.\[9,10,11\] Vildagliptin is potent inhibitor of DPP4 enzymes (concentration required to achieve 50% of DPP4 inhibition – IC 50). Vildagliptin are cleared from the plasma relatively quickly compared to other gliptins(EMEA).\[7\]

**Drug interaction profile**

Vildagliptin does not affect the drugs that are likely to be substrates for cytochrome p 450 enzymes. They are neither inhibitors nor inducers. No pharmacokinetic interaction has been found between vildagliptin and metformin (1000mg bid),\[6\] pioglitazone (45mg qd) or glibenclamide (10mg qd),\[12\] Antihypertensive agents such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers or calcium channel blockers, valsartan, ramipril and amlodipine,\[6\] simvastatin,\[13\] the cholesterol-lowering agent in studies in T2DM patients.

**MONOTHERAPY**

Treatment with vildagliptin showed an average decrease in HbA1c levels of 1.4% after 24 weeks as monotherapy in a subgroup of patients with no prior oral treatment and after a short period of time from the diagnosis of diabetes.\[14\]

Some study showed that treatment with vildagliptin for 4 weeks improves postprandial plasma triglyceride and apolipoprotein B-48–containing triglyceride-rich lipoprotein particle metabolism after a fat-rich meal in drug-naive patients with type 2 diabetes.\[15\] They found that DPP-4 inhibition, or pharmacological augmentation of GLP-1 receptor (GLP-1R) signaling, reduces intestinal secretion of triacylglycerol, cholesterol, and apolipoprotein B-48.\[16\]

The 4-week study assessed the effect of vildagliptin 100mg once daily or placebo on glycemic control, plasma glucagon, and insulin levels. Vildagliptin significantly reduced
fasting glucose and postprandial glucose (PPG) \((P < .037\) and \(P < .001\), respectively); also reduced HbA1c by 0.38% (\(P < .001\)) versus placebo. Glucagon levels were decreased and insulin levels were not significantly altered with vildagliptin versus placebo. Hypoglycemia did not occur in either group. Body weight showed increased by 0.12 kg in the placebo group and by 0.21 kg in the vildagliptin group, a nonsignificant difference. The authors concluded that vildagliptin improves metabolic control in association with reduced glucagon levels, improved glycemia, and unaltered insulin levels.\(^{[17]}\)

The study in some patients who were treated with vildagliptin 50 mg and 100 mg once daily experienced a decrease in HbA1c 0.43% (\(P = .003\)) and 0.40% (\(P = .004\)) respectively versus placebo.\(^{[18]}\) A significant decrease in PPG levels was observed in patients treated with vildagliptin 50 mg once daily versus placebo (\(P = .012\)). Although with vildagliptin 100 mg once daily versus placebo, this difference did not reach statistical significance. Hypoglycemic event rates were similar among all groups, including placebo, and rates were not dose related. Two cases of hypoglycemia were considered symptomatic, both of which occurred in patients taking vildagliptin. Treatment had a neutral effect on body weight throughout the trial and consistent with other studies.\(^{[19,20]}\)

Another study compared the efficacy and tolerability of vildagliptin with rosiglitazone in a 24-week, double-blind, randomized trial.\(^{[21]}\) Patients (N=786; baseline HbA1c, 8.7%) received either vildagliptin 100 mg daily or rosiglitazone 8 mg once daily. HbA1c levels decreased from baseline to a similar extent in the 2 groups. Vildagliptin decreased HbA1c by 1.1% ± 0.1% (\(P < .001\)), and rosiglitazone decreased HbA1c by 1.3% ± 0.1% (\(P < .001\)). These results demonstrated vildagliptin's noninferiority versus rosiglitazone. Patients in the rosiglitazone group were more likely to experience edema and increased body weight; these effects were not observed among patients in the vildagliptin group.

Patients treated with vildagliptin 50 mg plus metformin ≥1,500 mg/d and vildagliptin 100 mg plus metformin ≥1,500 mg/d once daily demonstrated a reduction in HbA1c of 0.7%±0.1% versus placebo (\(P < .001\)) 1.1%±0.1% versus placebo (\(P < .001\)) respectively. The authors concluded that vildagliptin produced meaningful decreases in HbA1c in patients whose diabetes was inadequately controlled with metformin. Body weight was unchanged relative to placebo in patients treated with vildagliptin 50 mg, but patients treated with vildagliptin 100 mg demonstrated an increase of 1.2 kg vs 0.4 kg relative to placebo. One patient in each group experienced a mild hypoglycemic event.\(^{[22]}\)
Random study of 592 Patients (mean baseline HbA1c, 8.7%) were treated with pioglitazone 30mg once daily, vildagliptin 100mg once daily, vildagliptin 100mg once daily plus pioglitazone 30mg once daily, or vildagliptin 50mg once daily plus pioglitazone 15mg once daily. Vildagliptin 100mg once daily plus pioglitazone 30mg once daily resulted in a statistically significant reduction in HbA1c levels compared with patients assigned to pioglitazone alone (1.9% vs 1.4%; *P*<.001). Although this abstract supports the efficacy of this combination, this information is limited by the inability to fully assess study quality and design.\[23\]

Another study randomized 256 patients (mean baseline HbA1c, 8.9%) currently taking insulin (mean daily dose, 82 units) to vildagliptin 50 mg twice daily or placebo in addition to their insulin therapy.\[24\] After 24 weeks, HbA1c had decreased by 0.5% ± 0.1% in the vildagliptin group compared with 0.2% ± 0.1% in the placebo group (*P*=0.022). In a subgroup analysis, patients aged ≥65 years who were treated with vildagliptin plus insulin experienced a 0.7% ± 0.1% decrease in HbA1c versus no change in patients treated with placebo (*P*<.001). The incidence of side effects was similar between the groups. Hypoglycemia was less common in the vildagliptin group (vildagliptin, 113 events; placebo, 185 events); this may reflect improved glucose sensitivity with vildagliptin. No changes in body weight were reported.

In one of the dose-finding study in Japanese patients (n=291), 12 weeks of vildagliptin 10, 25 or 50mg BID treatment significantly reduced HbA1c levels by 0.53%, 0.67% and 0.92% respectively (p<0.001 vs. placebo) from baseline levels of 7.4%.\[25\] A pooled analysis of five trials further confirmed that dosages of vildagliptin 50mg BID (n=1138) provides a significant (p<0.05) reduction of 1.0% from a mean baseline HbA1c of 8.7% after 24 weeks. In patients with baseline HbA1c>8%, reductions in HbA1c was 1.1% with vildagliptin 50mg BID and 1.7% with metformin 2000mg/day, whereas in patients with baseline HbA1c ≤8%, the reductions were 0.6% and 0.7% respectively.\[23\]

Decrease in mean FPG levels after 24 week treatment with vildagliptin 50mg BID were -0.856 and -1.255mmol/L and -1.056 and -0.555mmol/L with vildagliptin 50mg OD, which were significantly greater compared to placebo. Data from the pooled analysis of vildagliptin 50mg BID (n=1135) indicated a significant (p<0.05) reduction of 1.08mmol/L from a mean baseline FPG of 10.3mmol/L after 24 weeks.\[26\]
COMBINATION THERAPY

Addition of vildagliptin to metformin therapy in patients with inadequately controlled T2DM resulted in decreases of HbA1c and FBG of 0.7±0.1% and 14±5mg/dl respectively, 1.1±0.1% and 30±5 mg/dl, for the 50mg qd and 100mg qd treatment arms in one trial, after 24 weeks. 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 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.

In a comparative trial evaluating effect of vildagliptin 50mg BID to glimepiride up to 6mg OD on prandial glucagon levels, as add on therapy to metformin in T2DM patients inadequately controlled by metformin mono therapy. Prandial glucagon levels decreased by 3.4±1.6 pmol.h/L by vildagliptin (n=137) and increased by 3.8±1.7pmol.h/L by glimepiride (n=121), with between-group difference of 7.3±2.1 pmol.h/L (P<0.001). This established that vildagliptin 50mg significantly improves postprandial alpha-cell function when compared to SU glimepiride.

Galian trial compared efficacy and tolerability of vildagliptin 100mg with TZDs (agent and dose at the investigators discretion) as add on therapy to stable dose of metformin (≥1000mg/day), in T2DM patients with inadequately controlled HbA1c (7-10%). The mean change in HbA1c from baseline was -0.68±0.02% and -0.57±0.03% in vildagliptin and TZD group respectively. Between the groups difference was -0.11% (95%CI:-0.17% and -0.04%), establishing the non-inferiority of vildagliptin (p=0.001) after 3 months of treatment.

In a 52 week interim analysis of large randomized, double-blind, multicentre study, examining the efficacy and safety of vildagliptin vs. glimepiride as add-on therapy in patients inadequately controlled on metformin monotherapy (HbA1c 6.5-8.5%). Mean change from baseline HbA1c (7.3%) at week 52 endpoint was -0.44% (0.02%) and-0.53% (0.02%) with vildagliptin and glimepiride respectively, demonstrating non-inferiority of vildagliptin (97.5% CI; 0.02%, 0.16%), but a greater proportion of patients reached this target without hypoglycemia in the vildagliptin group (50.9 vs. 44.3%; p<0.01). Vildagliptin is not a substitute for insulin in insulin-requiring patients. Vildagliptin should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.
In vildagliptin plus insulin trial, subgroup analysis showed that patient age was an important factor in achieving glycemic control. Patients aged >65 years had a significant lowering of adjusted mean HbA1c levels (between-group difference vildagliptin 50mg BID vs. placebo – 0.6% [95% CI –1.0, –0.3; p=0.001]) unlike patients aged <65 years (–0.1% [95% CI –0.4, 0.1; p=0.361]) 61 and this effect was sustained in extension trial at week 52.[30]

**Role of Vildagliptin in diabetic dyslipidemia**

The characteristic features of diabetic dyslipidemia are a high plasma triglyceride concentration, low HDL cholesterol concentration and increased concentration of small dense LDL-cholesterol particles. Vildagliptin reduces circulating triglycerides and have an inhibitory effect on the lipoprotein metabolism by inhibiting the triglycerides absorption from the gut. It promotes sympathetically mediated lipid mobilization and catabolism in the post absorptive state.[31]

**Special patient populations**

Renal impairment does not alter the t½ of vildagliptin, but Cmax 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.[6]

**Chronic kidney disease**

Use in Patients with Chronic Kidney Disease, the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) defines CKD by the presence of kidney damage or a glomerular filtration rate (GFR) \60 \text{mL/min/1.73 m}^2\text{ for 3 months or more.}\[32\] Furthermore, many other common antidiabetes drugs are renally excreted and have a prolonged half-life in patients with CKD, thereby increasing the risk of hypoglycemia. The DPP-4 inhibitors can be used in patients with all degrees of renal insufficiency, including ESRD, although dosage reduction is needed for saxagliptin, sitagliptin and vildagliptin. Linagliptin can be used without adjustment, since it is not renally excreted. Individuals with concomitant T2DM and CKD may be receiving an ACEI for management of hypertension because this class of medications may reduce cardiovascular events and protect the kidney.[33] A small increase in the risk of angioedema has been observed in patients taking on current ACEI and vildagliptin, but the authors were unable to determine a class effect through review of post marketing surveillance data and the literature.[34] It is postulated that ACE inhibition
shifts the metabolism of the angioedema-associated vasoactive peptides bradykinin and substance P to the secondary DPP-4 pathway.

**Older people**

Clinical management of the older patient with T2DM is often challenging as these patients have an increased prevalence of cardiovascular risk factors, diabetes-related complications, and comorbidities such as renal impairment, congestive heart failure, cognitive impairment, and physical disability. A position statement issued by the International Association of Gerontology and Geriatrics (IAGG), the European Diabetes Working Party for Older People (EDWPOP), and the International Task Force of Experts in Diabetes, recommends that an HbA1c target range of 7.0–7.5% should generally be aimed for in older patients. A double blind, randomized, active-controlled study compared vildagliptin with metformin over 24 weeks in 335 drug-naive patients with T2DM aged ≥65 years. In this study, 41% of patients had normal renal function, 57% had mild renal insufficiency, and less than 2% had moderate renal insufficiency. The investigation showed that vildagliptin is an effective and well-tolerated treatment option in this group, demonstrating non-inferiority to metformin in terms of glycemic control, but superior gastrointestinal tolerability. The second trial, a double-blind, randomized, placebo controlled study of sitagliptin over 24 weeks in 206 patients with T2DM aged ≥65 years, concluded that sitagliptin significantly and rapidly improved glycemic control and was well tolerated in this group. This study also included patients with moderate renal insufficiency (22%), but excluded those with severe renal insufficiency (estimated creatinine clearance ≤35mL/min).

Recent evidence shows that T2DM is an independent risk factor for bone fracture and that older people with T2DM are at an increased risk of hip fractures. A Randomized, Double-Blind, Placebo-Controlled Trial demonstrated Vildagliptin was proved as an efficient and safety drug in New-Onset Diabetes after Kidney Transplantation patients.

**SAFETY PROFILE**

**Cardio and cerebrovascular safety**

A study conducted as per Food and Drug Administration, USA (USFDA) guidance, showed that vildagliptin does not lead to an increase in CCV events in a T2DM population. This meta-analysis was done with pooled the data from 25 phase III vildagliptin trials lasting from 12 weeks to over 2 years, where the drug was used either alone or in combination with other therapies. Patients received either a 50-mg dose of vildagliptin once daily (OD) (n = 1,393),
twice daily (BID) (n = 6,166) or active and placebo comparators (n=6,061), to evaluate CCV safety of vildagliptin. The RRs for both vildagliptin regimens were <1 (RR=0.88; 95% CI = 0.37, 2.11 for 50 mg OD and RR=0.84; 95% CI=0.62, 1.14 for 50 mg BID).

**Hepatic safety profile**

Another meta-analyses,[40] with pooled the safety data from 36 phase 2 and 3 clinical trials to investigate hepatic safety profile vildagliptin. The results from this meta-analysis showed that the greater proportion of vildagliptin recipients had mild elevations in liver enzymes versus comparator recipients (ALT/AST levels >= 3x upper limit of normal [ULN]). However, vildagliptin was not associated with an increased risk of having severely elevated liver enzymes (AST/ALT ≥10x ULN, or AST/ALT ≥3x ULN and bilirubin ≥2x ULN). Nor was vildagliptin associated with an increased risk of Hepatic adverse effects( AEs). Two patients experienced severe elevations in liver enzymes attributable to vildagliptin treatment. Both cases were asymptomatic and resolved upon discontinuation of treatment. Since a small number of these hepatic enzyme elevations were reported on vildagliptin as well, liver enzyme monitoring after initiation of therapy is prudent and consistent with the vildagliptin product information.

**Pancreatic safety profile**

Some study highlighted 81 pooled safety data from 24 phase 2 and 3 double-blind controlled clinical trials, to investigate its association with pancreatitis-related AEs.[41] The odds ratio for pancreatitis-related AEs was <1 for vildagliptin 50mg OD and BID (OR = 0.90 and 0.78, respectively), indicating no increased risk relative to all comparators. The result from this meta-analysis established that there was no evidence of an increased risk of pancreatitis related AEs following treatment with vildagliptin at the marketed doses of 50mg OD and BID relative to the all comparators group.

**Hypoglycemia**

The incidence of hypoglycemia reported by vildagliptin monotherapy were low and similar to that with metformin or rosiglitazone, (≤0.7% vs. ≤0.4% in metformin, 0.04% in rosiglitazone and 0% in placebo recipients).[42] Moreover, when used in combination with insulin, vildagliptin 50mg BID resulted in a significant (p<0.001) reduction in the frequency of hypoglycemic events compared with placebo.[22]

**Gastrointestinal diseases**
The frequency of reported GI AEs with metformin 2000mg daily were twice than that of recipients of vildagliptin 50mg BID (43.7% vs. 21.8%; p<0.001).\[43\] This resulted in 3-4 times higher incidence of diarrhoea, nausea, abdominal pain, dyspepsia and flatulence with metformin than with vildagliptin Also incidence of GI AEs was considerably lower in vildagliptin 50mg OD plus metformin (≥1500 mg/day) recipients (p=0.022), when compared to placebo plus metformin recipients.\[21\] The occurrence of GI-related AEs in acarbose recipients was more than twice than that in vildagliptin recipients (25.5% vs. 12.3%;p<0.001).

**Pregnancy and lactation**

There are no adequate data on the use of Vildagliptin in pregnant women, hence the potential risk for humans is unknown. Due to lack of data, Vildagliptin should not be used during pregnancy. Animal studies have shown excretion of Vildagliptin in milk; it is not known whether this is the case in humans, therefore Vildagliptin should not be used during lactation.\[29\]

**Bodyweight**

The DPP-4 inhibitor vildagliptin appear to be bodyweight neutral, as change in bodyweight associated with vildagliptin treatment is neutral or modest in nature and not significantly different from placebo.\[21\] In addition to this, the occurrence of cardiac AEs (including arrhythmias and conduction abnormalities) and hypertension with vildagliptin was comparable to placebo and also less than with metformin.\[44\] Vildagliptin is currently approved in Latin America, Asia and Asia pacific region, all countries of European Union (in combination with metformin, SUs and TZDs) for the treatment of T2DM. The recommended daily dose of vildagliptin is 100mg, administered as one dose each of 50mg in morning and evening. When used in dual combination with a SU, the recommended dose of vildagliptin is 50mg OD administered in the morning. Drug can be administered with or without meals.

**Pharmacoeconomics of Vildagliptin**

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.\[45\]
CONCLUSION
Vildagliptin is an orally active, potent and selective Dipeptidyl Peptidase-4 (DPP-4) inhibitor approved by US FDA in February 2007. It is well tolerated by elderly patients with type 2 DM. It has got cardiovascular and renal safety profile. It significantly reduces glycosylated hemoglobin HbA1C, OHA fasting plasma glucose and postprandial plasma glucose levels. It also improves the β cell function on the basis of pharmacodynamic modeling and sensitivity of alpha cells to glucose for both suppressive as well as stimulatory effect. It does not affect the gastric emptying and has got good gastrointestinal safety and weight neutrality effect. When administered as monotherapy or combination therapy with OHA or insulin in patients with type II DM. Numerous long term clinical trials demonstrated with vildagliptin once daily or twice daily is effective, safe and well tolerated in patients with type II diabetes mellitus.

REFERENCES


