

## Efficacy and safety of Vildagliptin in the management of type 2 Diabetes Mellitus

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### ABSTRACT

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Type 2 diabetes mellitus (T2DM) is epidemic in most developed and many developing countries and is a leading cause of morbidity and mortality. Vildagliptin represent a new class of oral anti-diabetic agent that enhance the action of incretin hormone through inhibition of Dipeptidyl peptidase-4. The enhancement of incretin hormone (GLP-1 & GIP) potentiates the insulin secretion in  $\beta$ -cells and suppresses the glucagon release by  $\alpha$ -cells in the pancreas. The present article reviews the impact of DPP-4 inhibitor, Vildagliptin in monotherapy as well as combination with a special emphasis on the Risk & Benefits on different organs of T2DM patients. Literature was searched on PubMed related to safety and efficacy of vildagliptin that include all the observational and interventional studies. Vildagliptin is a potent & specific DPP-4 inhibitor that has demonstrated weigh neutrally, and improves  $\beta$ -cell as well as cardiovascular function in patient with DM type 2 in multiple monotherapy & combination. However, hypoglycaemic event reported with combination of metformin, rosiglitazone and SU, but safe with pioglitazone, while in combination with insulin the event was found to be reduced. Vildagliptin also shows feedback inhibition of GLP-1 secretion which reduces risk of cardiovascular and hypoglycaemia, whereas it concern to increasing the risk of pancreatitis according to post marketing surveillance.

**Keywords:** Vildagliptin; DPP-4 inhibitor; T2DM; Incretin hormone; GLP-1 & GIP

### INTRODUCTION

The DPP-4 inhibitor Vildagliptin is used for the treatment of type 2 diabetes mellitus (T2DM). It is a potent, selective and orally active 2nd generation inhibitor of DPP-4, with a reversible and competitive mechanism of action that binds and forms a complex with DPP-4, causing its inhibition.<sup>1</sup> This results in improved glycaemic control as determined by glycosylated haemoglobin (HbA1c) and fasting plasma glucose (FPG) levels plus an enhancement of pancreatic  $\alpha$  and  $\beta$ -cell functions.<sup>2</sup> Vildagliptin was approved in Feb 2008 by European Medicines Agency for use within the EU<sup>3</sup> and is also available on the Latin American and Asia-Pacific markets.<sup>4,5</sup> Until July 2011 Vildagliptin had been approved in 86 countries and launched in 43 countries.<sup>4</sup> Several DPP-inhibitors have been approved by the US Food and Drug Administration (FDA) for the treatment of type 2 diabetes mellitus but Vildagliptin is still undergoing evaluation and has not yet been approved in the United States (Table 1).<sup>6</sup> In India Vildagliptin is available in the brand name of *Galvus*, *Jalra* and *Zomelis*. This article examines the impact of DPP-4 inhibitor Vildagliptin in monotherapy as well as combination with a special emphasis on the risk & benefits of the different organs of T2DM patients.

### Mechanism of action:

The administration of vildagliptin results in a rapid and complete inhibition of DPP-4 activity, resulting in increased the amount of two incretin hormones found in the body, called glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). This allows for increased insulin sensitivity, decreased glucagon secretion and reduces sugar level in blood. Vildagliptin bind to DPP-4 and inactivated it due to this GLP-1 Active and work to enhance the  $\beta$ -cell sensitivity as well as reduce  $\alpha$ -cell sensitivity, which cause increase the amount of insulin and decrease the amount of glucagon respectively and finally glucose level reduce in blood. (Fig.1).

Vildagliptin also showed efficacy in reducing HbA(1c) levels in patients with type 2 diabetes when used in combination with metformin, pioglitazone or insulin. Vildagliptin was generally well tolerated when administered alone or in combination with additional antidiabetic treatment.

Initially, patients with type 2 diabetes may be able to control their blood glucose levels with diet and exercise alone. However, many people with diabetes progress to require antidiabetic medications. Currently, there are five classes of oral glucose lowering drugs available that may be used as a monotherapy or in combination. The mechanism of action and the risks and benefits of DPP-4 inhibitor indicated in Fig. 2.

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Fig.1: Efficacy and safety of Vildagliptin in the management of type 2 DM

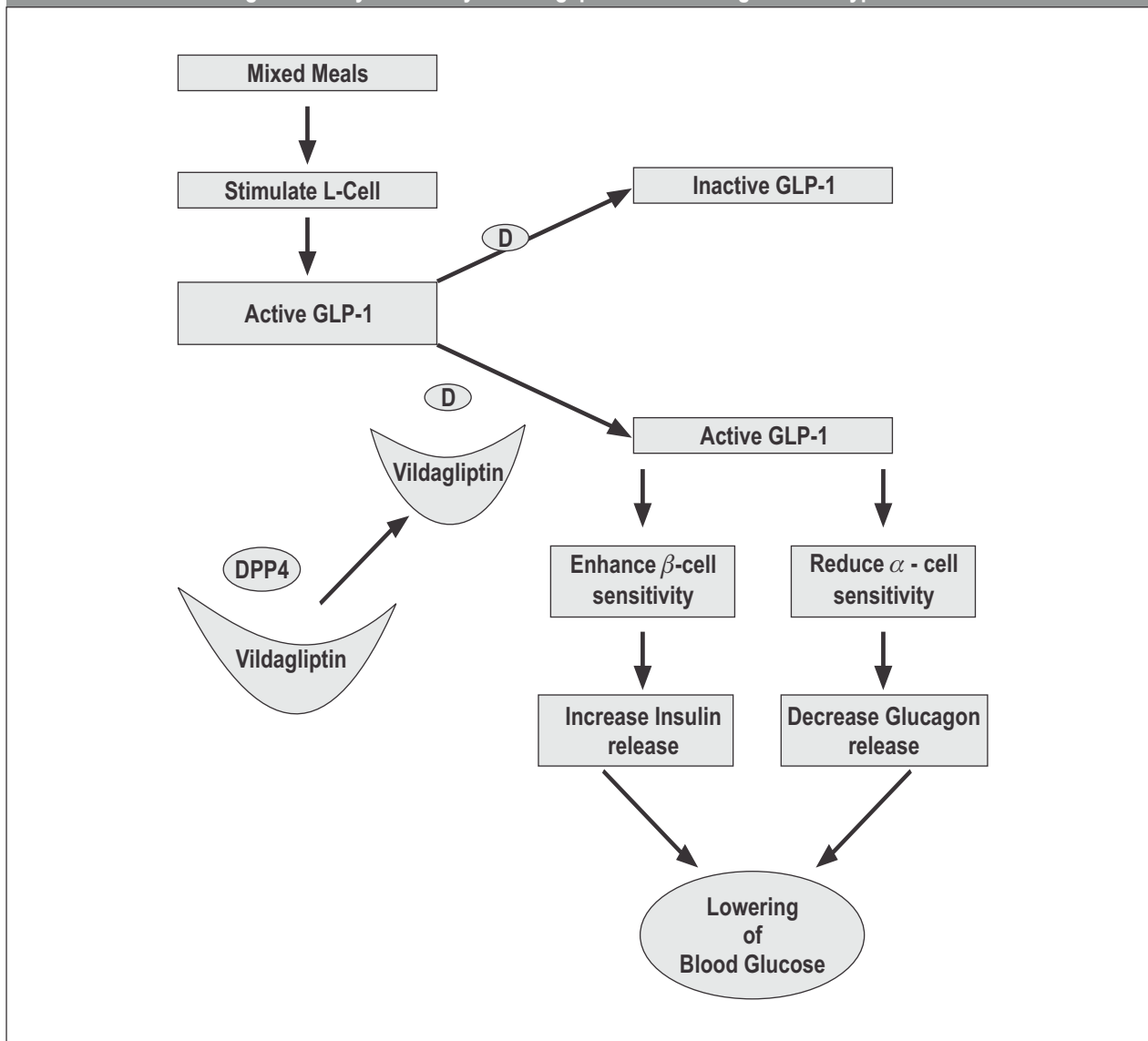
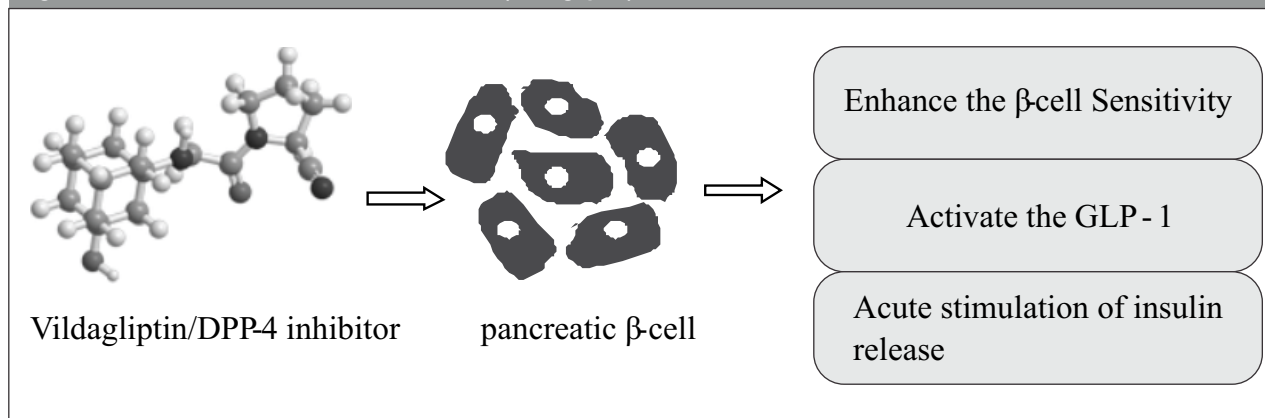
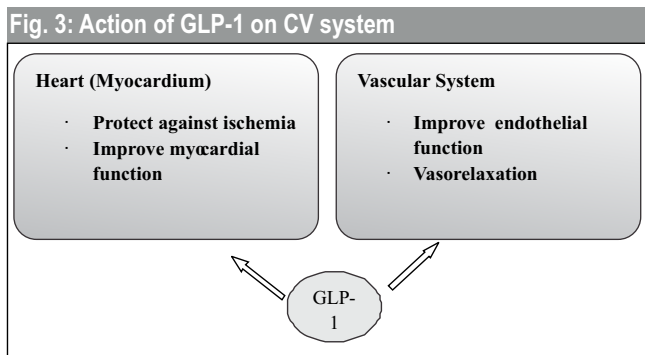


Fig. 2: Mechanism of action of DPP-4 inhibitor (Vildagliptin)





### Effect on Body Weight:

Overweight and/or obesity increase the risk of developing type 2 diabetes, and confound glycaemic control once the disease develops.<sup>8</sup> A several studies on the influence of DPP-4 inhibitors on patient weight demonstrated variable results but are generally considered to be neutral. A studies regarding treatment with Sitagliptin showed variability between 1.5 kg of weight loss in 52 weeks of therapy to 1.8 kg of weight gain in 24 weeks of therapy, whereas treatment with Vildagliptin showed variability between 1.8 kg of weight loss to 1.3 kg of weight gain in 24 weeks of therapy & similar studies with Saxagliptin showed variability between 1.8 kg of weight loss to 0.7 kg of weight gain in 24 weeks of therapy. In a meta-analysis of 13 studies regarding the treatment of all three DPP-4 inhibitors, the effect of this group of drugs on weight was neutral.<sup>9,10</sup>

In a single-centre, randomized trial, in type 2 diabetic patients randomized to Vildagliptin (50 mg bid) or placebo underwent a fat tolerance test at baseline and at the conclusion of a four-week follow-up period, The fat tolerance test entailed consumption of a standardized fat-rich meal followed by assessment of multiple lipid, lipoprotein, and apolipoprotein parameters.<sup>11</sup> In a other randomized clinical trial in patients with relatively low baseline glycaemic values (mean HbA1C 7.3%, fasting plasma glucose [FPG] 9.2 mmol/L [165 mg/dL]), patients inadequately controlled on metformin who were randomized to Vildagliptin 50 mg bid were weight stable for 52 weeks (-0.2 kg), which was highly significant as compared with the weight gain seen in the comparator group receiving glimepiride 6mg daily between-group difference 1.8 kg,<sup>12</sup> whereas a two-year randomized trial of Vildagliptin monotherapy in patients with mild baseline hyperglycaemia (HbA1C 6.6%, FPG 6.9 mmol/L [124 mg/dL]), patients randomized to Vildagliptin achieved a mean 1.1 kg weight loss, which was statistically significant ( $P = 0.026$ ) versus baseline.<sup>13</sup> A comparable study with rosiglitazone or metformin in drug-naïve patients, Vildagliptin monotherapy achieved comparable levels of glycaemic efficacy, with no

changes in weight by the end of the studies. In contrast, patients receiving rosiglitazone experienced statistically significant weight gain, while patients receiving metformin lost weight.<sup>14,15</sup> The use of Glitazones is also associated with weight gain, as documented in several clinical trials. Body weight was increased by 4 kg in 3 years with pioglitazone in the PROACTIVE study<sup>16</sup>, while the use of rosiglitazone produced a weight gain of 5 kg in 5 years in the ADOPT study<sup>17</sup> and 2 kg in 3 years in the DREAM study.<sup>18</sup>

More recently, the results of the ACCORD trial showed that intensive therapy aiming at an HbA1c target of <6.0% was associated with a weight gain of more than 10 kg in 27.8% of the patients.<sup>19</sup>

In summary Metformin in monotherapy as well as in combination induced weight loss, while combination with Vildagliptin weight neutrally. In the case of Rosiglitazone, Sitagliptin, Saxagliptin, glimepiride induced weight gain. Vildagliptin improves the sensitivity of the  $\alpha$ -cell to glucose; the sulfonylurea reduces it, leading to a more robust glucagon counter regulatory response with vildagliptin<sup>14</sup> Vildagliptin is a potent and specific DPP-4 inhibitor that has demonstrated weight neutrality in patients with DM type -2 in multiple monotherapy and in combination. Several recently identified mechanisms reveal the weight neutrality, and in some cases weight loss, associated with Vildagliptin.

### Cardiovascular safety

In the past, several studies have found that certain anti diabetes drugs may cause increased cardiovascular (CV) risks. An experimental study has shown that GLP-1 has several potentially beneficial actions on cardiovascular risk. (Fig.3) Some of those, such as protection from myocardial ischemic damage and improvement of cardiac function have also been demonstrated in humans. However, the equivalence of GLP-1 agonists and DPP-4 inhibitors with GLP-1, with respect to cardiovascular risk profile, cannot be assumed or taken for granted. Drugs of those two classes have been shown to effectively reduce glycosylated haemoglobin and to have a specific effect on post-prandial glucose,<sup>20</sup> and a Multi-centre, Randomized, Double-blind, Placebo-controlled Clinical Trial to Evaluate the Effect of 52 Weeks Treatment With Vildagliptin on Left Ventricular Function in Patients With Type 2 Diabetes and Congestive Heart Failure. Effect on HbA1c and overall safety and tolerability will also be assessed.<sup>21</sup>

According to study on T2DM patients compared the CV effects in individuals treated with either metformin or SU. Which found an increased likelihood of death from any cause in the patients treated with SU (24-61% increased risk depending on the specific drug), along with an increased risk

of congestive heart failure (18-30%), whereas treatment with Rosiglitazone Monotherapy was found to be associated with higher risk for any CV event.<sup>22</sup>

A new study has found that SUs increase the risk of both CV and all-cause mortality. The researchers found higher daily doses of first and second-generation SUs increased mortality risk by more than 200% and 30%-40% respectively.<sup>23</sup> The new oral antidiabetic drugs Vildagliptin and Sitagliptin work by boosting the gut's incretin hormones GLP-1 and GIP to regulate insulin secretion following food intake and glucagon secretion when blood sugar is low. Their action seems to be merely to enhance a natural process & comparable study with incretin Mimetics listed in Table-2. There is considerable preclinical evidence that DPP-4 inhibitors, which act by increasing plasma levels of active GLP-1, may actually exert cardio-protective effects, also limited human studies that are available have suggested that GLP-1 may improve CV function.<sup>24,25</sup>

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.<sup>26</sup> In a large meta-analysis, Vildagliptin was not associated with an increased risk of adjudicated CCV events relative to all comparators in the broad population of type 2 diabetes including patients at increased risk of CCV events.<sup>27</sup> Vildagliptin vs. all comparators were consistent across subgroups, that is, under age 65 years and above, female and male, and with or without previous history of CCV events. A noteworthy finding was that the RR for any adjudicated CCV event in patients in the high CV risk subgroup (i.e. patients with prior history of CCV events), with understandably, a much higher event rate than in the lower risk subgroup (no prior history of CCV events) was below 1 [RR = 0.78; 95% CI (0.51, 1.19)]. Consistent results were also seen in the subset of studies with a duration  $\geq$  52 weeks, further strengthening a conclusion that Vildagliptin does not increase CCV risk.<sup>28</sup> There is substantial preclinical evidence that DPP-4 inhibitors, which act by increasing plasma levels of active GLP-1, and injectable incretin mimetics, may actually exert cardio protective effects<sup>29</sup> and the limited human studies that are available have suggested that GLP-1 may improve CV

function.<sup>30-31</sup> A study by Kothny et al on the cardiovascular safety profile of Vildagliptin included data from 19 trials of up to 24 weeks duration, including 11 monotherapy trials and 8 of combination therapy with metformin, Thiazolidinedione's and SUs. Analysis included subcategories of pre-defined cardiac vascular, cerebrovascular and peripheral vascular events. Data from a total of 6063 patients exposed to Vildagliptin (1469 on 50mg daily and 4594 on 50mg bid) and 5661 on placebo or comparator drugs (metformin, SUs and TZDs) were included. The majority of patients (>70%) were Caucasians with a BMI of 31, a mean disease duration of 4 years and a mean duration of exposure to Vildagliptin of 21 weeks. The study shows the overall incidence of cardiovascular events for Vildagliptin 50mg OD and BID was lower when compared to placebo or all comparators combined (0.88% and 1.02% vs. 1.15% and 1.29%). The same held for serious adverse cardiovascular events (0.54% and 0.54% vs. 0.69% and 0.78%). Eleven myocardial infarcts (2 acute) occurred among patients taking Vildagliptin; of these, 9 (0.2%) were in the 50mg bid group. Eight MIs (0.1%), including 3 acute MIs in the comparator group, occurred in the placebo and comparator groups combined. Nine patients of the 6000 on Vildagliptin developed coronary artery disease compared with 16 of a similar sized group on placebo or comparator drugs. There were 6 CVAs in the Vildagliptin 50 m bid groups (0.1%) and the same proportion (0.1%) in the placebo and comparator groups.<sup>32</sup>

In summary there are no signals to cause concern about cardiovascular safety with Vildagliptin in monotherapy as well as in combination with Rosiglitazone, Sitagliptin, Saxagliptin, Thiazolidinedione's, glimepiride. Vildagliptin is a potent and specific DPP-4 inhibitor that has demonstrated to improve CVD in patients with DM type -2 in multiple monotherapy and combination.

### Hypoglycaemia

After the failure of monotherapy with metformin, clinicians are offered different options to intensify treatment, including sulfonylurea, Glitazones, and insulin. However, all these classes of drugs show side effects that can limit their use. Hypoglycaemia has a substantial impact in terms of mortality,

**Table 1: Characteristics & Approval of different DPP-4 Inhibitors**

Molecules	Brand Name	Manufacturer	Composition	Doses	FDA/EMA Approval
Vildagliptin	Galvus	Novartis	Monotherapy or in combination	25-200mg	Revision/Yes
Sitagliptin	Januvia	Merck Sharp & Dhome	Monotherapy or in combination	100 mg	Yes/Yes
Saxagliptin	Onglyza	Bristol- Myers squibb	Monotherapy or in combination	2.5-5mg	Yes

morbidity, and quality of life.<sup>33</sup> One out of four patients with T2DM treated with insulin for >5 years experiences at least one episode of severe hypoglycaemia, and the frequency of episodes increases with increasing age and diabetes duration.

Mild hypoglycaemia in type 2 diabetic patients on insulin for <2 years was less frequent than in type 1 patients with <5 years disease duration (mean rate: 4 vs. 36 episodes per subject-year,  $p < 0.001$ ). In type 2 diabetic patients treated with sulfonylureas or insulin for <2 years, no differences were observed in the proportion experiencing severe hypoglycaemia (7 vs. 7%, difference is 0 [95% CI: -7 to 9%]), mild symptomatic (39 vs. 51%, difference 12 [-3 to 25%]) or interstitial glucose <2.2 mol/l (22 vs. 20%, difference 2 [-13 to 10%]). Severe hypoglycaemia rates were comparable in patients with type 2 diabetes on sulfonylureas or insulin < 2 years (0.1 and 0.2 episodes per subject-year) and far less frequent than in type 1 diabetes (<5 years group, 1.1; >15 years group, 3.2.episodes per subject-year).<sup>34</sup>

The incidence of hypoglycaemia reported by Vildagliptin monotherapy were low and similar to that with metformin or rosiglitazone, ( $\leq 0.7\%$ 50,53,56 vs.  $\leq 0.4\%$ 53 in metformin, 0.04% in rosiglitazone and 0% in placebo56 recipients).<sup>35</sup> However combination with metformin, one hypoglycaemia event each was reported from Vildagliptin 50 mg OD and BID recipient<sup>36</sup> and one recipient of Vildagliptin 50mg BID experienced three hypoglycaemic events (vs. no events with pioglitazone).<sup>37</sup> Moreover, when used in combination with insulin, Vildagliptin 50 mg BID resulted in a significant ( $p<0.001$ ) reduction in the frequency of hypoglycaemic events compared with placebo.<sup>38</sup> The combination of Glibenclamide with the DPP-4 inhibitor Vildagliptin does not provoke more hypoglycaemia after oral glucose than does Glibenclamide alone. A single dose of Vildagliptin administered before an oral glucose load greatly reduces the total GLP-1 secretory response, suggesting feedback inhibition of GLP-1 secretion involving sensing of intact, biologically active GLP-1.<sup>39</sup>

In summary there are no signals to cause concern about Hypoglycaemia with Vildagliptin in monotherapy but signals have been reported in combination with Metformin, Rosiglitazone and Sulfonylurea. While no hypoglycaemic event has been reported in combination with pioglitazone, however combination with insulin (50 mg BID) reduces hypoglycaemic event. In patients with diabetes, treatment with the DPP-4 inhibitor Vildagliptin reduces fasting and postprandial glucose concentrations, suppresses meal-related glucagon responses, and enhances insulin secretion relative to ambient glucose concentrations<sup>40,41,42</sup> and also concern with feedback inhibition of GLP-1 secretion.

**Table 2: Comparison of Incretin Enhancers and Incretin Mimetics**

Incretin Enhancers	Incretin Mimetics
<b>Differences</b>	
Orally available	Injectable
Multiple targets	Single known target
GLP-1 PK favourable	Higher levels of GLP-1
Short vs. long acting	Longer acting, days–weeks
Drug overdose nontoxic	Drug overdose, a concern
Mild CNS side effects	Potential for side effects
Mild nausea and vomiting	Increased levels of nausea and vomiting

**Table 3: Most commonly reported ADRs associated with Vildagliptin in VigiBase.<sup>53</sup> (WHO Pharmacovigilance data base)**

WHO-ART preferred term	Number of reports*
Hyperglycaemia	61
Medicine ineffective	41
Dizziness	38
Headache	34
Hypoglycaemia	33
Abdominal pain	29
Diabetes mellitus aggravated	28
Nausea	28
Malaise	23
Hypertension	21
Rash	21
Pancreatitis	19
Asthenia	18
Fatigue	16
Oedema peripheral	16
Constipation	14
Pruritus	13
Weight decrease	13
Diarrhoea	12
Dyspepsia	12
Face oedema	12
Angioedema	10
Vomiting	10
Anorexia	10

\*Note that each report can be represented more than once in the table.



## Pancreatitis

It was reported earlier that T2DM has also been associated with increased risk of pancreatitis, such as cholelithiasis, hypertriglyceridemia are risk factors for acute pancreatitis.<sup>43</sup> While several large clinical studies have demonstrated the efficacy and safety of Vildagliptin in the management of type 2 diabetes mellitus. Unlike the older DPP-4 inhibitor, Sitagliptin and Vildagliptin has not been associated with the development of acute pancreatitis in post marketing reports.<sup>44</sup>

In a meta-analysis of pooled data from 38 phase of 2<sup>nd</sup> and 3<sup>rd</sup> clinical trials, the newer DPP-4 inhibitor Vildagliptin did not result in a greater incidence of acute pancreatitis when used for periods of 12 weeks to 2 years.<sup>45</sup> A single case of acute pancreatitis reported in post marketing survey with a 61-year-old woman who presented with severe abdominal pain was found to have acute pancreatitis. This occurred 5 weeks after the commencement of Vildagliptin, for the treatment of type 2 diabetes mellitus. The patient's pancreatic enzymes were elevated (amylase, 1205 U/L; lipase, 8846 U/L), and abdominal computed tomography demonstrated diffuse pancreatic swelling, cyst formation, and necrosis in the body of the pancreas (<3000 U/L).<sup>44</sup> However, between October 2006 and February 2009, there were 88 post marketing reports of severe pancreatitis in patients receiving Sitagliptin, prompting the US Food and Drug Administration to issue an alert on this potential adverse reaction.<sup>46</sup>

In summary this is controversial because the incidence of pancreatitis is generally higher in persons with type 2 diabetes mellitus and a direct independent causative effect of DPP-4 inhibitors is therefore difficult to establish.<sup>47,48,49</sup> Pancreatitis was recently (2010) added to the European SPC as a spontaneously reported post-marketing adverse event.<sup>6</sup>

## Other Adverse Events

Generally Vildagliptin showed mostly mild and transient adverse reaction. However some new signals has been listed in 'WHO Signal December 2011', which are dizziness(Common), hypoglycaemia, headache, oedema peripheral, constipation, arthralgia (Uncommon), upper respiratory tract infection, nasopharyngitis (very rare), abnormal liver function tests, hepatitis, urticaria, pancreatitis (Post marketing Survey).<sup>50</sup> The most frequently reported ADRs in association with Vildagliptin are listed in Table 3. A case of dry cough has been reported in India (Post marketing Survey).<sup>51</sup> the most frequently reported ADRs in association with Vildagliptin worldwide are listed in Table-3.

## CONCLUSION

Vildagliptin is a potent & specific DPP-4 inhibitor that has demonstrated weigh neutrally, and improves B-cell as well as CV function in patient with DM type 2 in multiple

monotherapy & combination. However hypoglycaemic event reported with combination of metformin, rosiglitazone & SU, but safe with pioglitazone, while combination with insulin reduced it. Vildagliptin also shows feedback inhibition of GLP-1 secretion which reduces risk of CV & hypoglycaemia, whereas it concern to increasing the risk of pancreatitis according to post marketing surveillance. Further large post marketing surveillances study is warranted to identify the pancreatitis due to Vildagliptin.

## Abbreviation

DPP-4: Dipeptidyl Peptidase-4

HbA1c: Haemoglobin A1c

FPG: Fasting Plasma Glucose

GLP-1: Glucagon like Peptide-1

GIP: Glucose-dependent Insulinotropic Peptide

EU: European Union

CV: Cardio Vascular

CCV: cardiovascular & Cerebrovascular

CVD: Cardiovascular Disease

BMI: Body Mass Index

CI: Confidential Interval

MI: Myocardial Infarction

DM: Diabetes Mellitus

T2DM: Type 2 Diabetes Mellitus

Sus: Sulphonylurea's

TZDs: Thiazolidinedione's

OD: Omne in die (Ones a day)

BID: Bis in die (twice a day)

P: Probability

RR: Risk Ratio

ACCORD: Action to Control Cardiovascular Risk in Diabetes

DREAM: Diabetes Reduction Assessment with Ramipiril and Rosiglitazone Medication

ADOPT: A Diabetes Outcome Prevention Trail

PROACTIVE: Prospective Pioglitazone Clinical Trial in Macrovascular Events

SPC: summary of Product characteristics

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