SAFETY AND TOLERABILITY OF VILDAGLIPTIN IN CLINICAL PRACTICE: NEWER PROMISING GLIPTIN FOR TYPE 2 DIABETES MELLITUS

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ABSTRACT
The prevalence of type 2 diabetes (T2DM) increases with age. Older patients have an increased likelihood for T2DM-related morbidity and mortality. The dipeptidyl peptidase-4 inhibitor vildagliptin is approved for use as monotherapy and combination therapy in type 2 diabetes mellitus. This article reviews the clinical efficacy and tolerability of vildagliptin in the treatment of type 2 diabetes, as well as summarizing its pharmacological properties. Improvements in glycaemic control were also seen with vildagliptin in elderly patients with type 2 diabetes and in patients with type 2 diabetes and moderate or severe renal impairment. Vildagliptin was generally well tolerated in patients with type 2 diabetes, was weight neutral and was associated with a low risk of hypoglycemia, reflecting its glucose-dependent mechanism of action. The elderly population with T2DM poses unique treatment challenges and have not been particularly well-represented in clinical trials, highlighting the need for additional studies to better define appropriate glucose targets and to ascertain the best strategies for achieving and maintaining appropriate glycaemic levels. In conclusion, vildagliptin is an important option for use in combination with metformin, a sulfonylurea or a thiazolidinedione in patients with type 2 diabetes who require combination therapy.

Keywords: DPP-4 inhibitors, Elderly, Oral hypoglycemic agents, Type 2 diabetes, Vildagliptin

Introduction
Diabetes mellitus is a disorder in which blood sugar (glucose) levels are abnormally high as the body does not produce enough insulin. Type 2 diabetes mellitus (T2DM) affects over 300 million people worldwide. The global prevalence of T2DM was estimated to be 9% in adults aged over 18 years. Diabetes is the fifth cause of death for women and the fourth for men in the USA. Inadequate control of blood glucose in patients correlates with a higher risk for diabetes-related micro and macro vascular complications[1]. Type 1 diabetes results from the pancreas's failure to produce enough insulin due to loss of beta cells, previously referred as “insulin-dependent diabetes mellitus” (IDDM) or “juvenile diabetes”. The loss of beta cells is caused by an autoimmune response. The cause of this autoimmune response is unknown. Type 2 diabetes 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, previously referred as "noninsulin-dependent diabetes mellitus” (NIDDM) or "adult-onset diabetes". The most common cause is a combination of excessive body weight and insufficient exercise. Gestational diabetes occurs due to presence of high blood glucose level during pregnancy. As pregnancy progresses, the developing baby will have a greater need for glucose. Hormone changes during pregnancy also affect the action of insulin that leads to hyperglycemia. Maturity onset diabetes of the young is a rare autosomal dominant inherited form of diabetes, due to single-gene mutations, causing defects in insulin production. It is significantly less common constituting only 1% to 2% of all cases[2].

Following risk factors may increase chance of getting diabetes:
1) Family history of diabetes.
2) Personal history of gestational diabetes (for females).
3) African, Hispanic, American, or Pacific Islander.
4) Injury to the pancreas (infection, tumor, surgery or accident).
5) Autoimmune diseases.
6) Age (risk increases with age).
7) Physical stress (such as surgery or illness).

Other risk factors that might be controlled:
1) High blood pressure.
2) Abnormal blood cholesterol or triglyceride levels.
3) Smoking.
4) Being overweight.
5) Use of certain medications like steroids.
Clinical manifestations:
The classic symptoms of untreated diabetes are unintended weight loss, polyuria (increased urination), polydipsia (increased thirst) and polyphagia (increased hunger). Symptoms may develop rapidly (weeks or months) in type 1 diabetes, while they usually develop much more slowly in type 2 diabetes. In addition, other clinical manifestations include blurred vision, headache, fatigue, slow healing of cuts and itchy skin. A number of skin rashes can occur in diabetes patients known as diabetic dermades. Prolonged high blood glucose can cause glucose absorption in the lens of the eye, which leads to changes in its shape, resulting in vision changes. Most people also suffer from symptoms due to low blood sugar (hypoglycemia), if blood sugar is less than 70 mg/dl. Weakness, dizziness, sweating, pounding heart, pale skin, poor coordination, bad dreams, nightmares, numbness in mouth and tongue3.

Diagnostic parameters:
The fasting blood glucose (sugar) test is the preferred way to diagnose diabetes. It is easy to perform and convenient. After the person has fasted overnight (at least 8 hours), a single sample of blood is drawn and sent to the laboratory for analysis. This can also be done accurately in a doctor's office using a glucose meter. Normal fasting blood glucose levels are less than 100 milligrams per deciliter (mg/dl). Fasting blood glucose levels of more than 126 mg/dl on two or more tests on different days indicate diabetes. A random blood glucose test can also be done to diagnose diabetes. A blood glucose level of 200 mg/dl or higher indicates diabetes. When fasting blood glucose stays above 100mg/dl, but in the range of 100-126mg/dl, this is known as impaired fasting glucose (IFG). While patients with IFG or prediabetes do not have the diagnosis of diabetes4.

Pathogenesis of type 2 diabetes mellitus
The natural history of T2DM as proposed originally of Ralph Defranzo (triumvirate theory) involved. Insulin resistance at level of liver resulting in hepatic outpouring of glucose into the hepatic venous system. Insulin resistance at peripheral tissue (skeletal muscles) resulting in inability in uptake of glucose. Beta-cell failure (five stages) resulting in declining insulin secretion capacity. Beta cells failure can be described in five stages:

Stage 1:
Beta-cell compensation, where the beta cell mass increases. This causes increased basal insulin release so that plasma glucose can be kept within the normal range. This beta-cell compensation occurs because of increasing insulin resistance (obesity and genetic factors). At this stage, people are usually obese with normal glucose tolerance and reduced insulin sensitivity by approximately 29%. It has been shown that 66% of beta-cell function is lost when the 2-hour post-meal plasma glucose is between 120 and 139 mg/dl (normal glucose tolerance) suggesting that beta cell dysfunction starts very early.

Stage 2:
Beta-cell adaptation, where in plasma glucose although higher than at stage 1 is associated with normal glucose tolerance, at the cost of increased workload. This stage is associated with a further decline in insulin sensitivity by 28% (as age advances and obesity worsens).

Stage 3:
Beta-cell decompensation, where in glucose levels rise relatively rapidly. At this stage, 80% of [beta]-cell function is lost. Fasting hyperglycaemia of approximately 140-200 mg/dl can result from basal hepatic glucose production of ~0.5 mg/kg/min due to associated insulin resistance. The liver of an 80-kg diabetic can add as much as 35 g of glucose to the systemic circulation following an overnight fast.

Stage 4:
Beta-cell decompensation (stable), once the plasma glucose rises it stays relatively stable.

Stage 5:
Beta-cell failure, marked by severe hyperglycaemia and progression to ketosis5.

Treatment:
Table 1: Oral Hypoglycaemic Agents (OHA)

| CLASS                  | EXAMPLES                | MECHANISM                                      |
|------------------------|-------------------------|------------------------------------------------|
| Biguanides             | Metformin               | Decrease hepatic gluconeogenesis               |
| Sulfonylureas          | Glipizide, Glimepiride  | Increase insulin secretion                      |
| Thiazolidinediones     | Pioglitazone, rosiglitazone | Increase insulin sensitivity in muscles & fats |
| Meglitinides           | Repaglinide, Nateglinide | Increase insulin secretion                      |
| Alpha glucosidase inhibitors | Acarbose, Miglitol      | Decrease intestinal absorption of carbohydrates |
| DPP4 inhibitors        | Vildagliptin, Sitagliptin | Increase insulin secretion                      |
| Incretin mimetics      | Exenatide               | Increase insulin secretion                      |

**Dipeptidyl Peptidase-4 Inhibitors (Gliptins):**

This new class of anti-diabetic agents seems like they have revolutionized the treatment of diabetes. Although various DPP-4 inhibitors have different pharmacokinetic and pharmacodynamic profiles, they are remarkably similar with regards anti-hyperglycaemic properties with a very safe adverse effect profile (weight neutral without causing hypoglycaemia). A list of available and expected gliptins are as follows:

- Sitagliptin (Merck Sharp and Dohme Corp, approved as Januvia by US FDA in year 2006)
- Vildagliptin (Novartis, approved as Galvus by EU in year 2007)
- Saxagliptin (Bristol-Myers Squibb, approved as Onglyza by US FDA in year 2011)
- Linagliptin (Boehringer Ingelheim, approved as Tradjenta by US FDA in year 2011)
- Alogliptin (developed by Takeda Pharmaceutical Company Limited, approved for use in Japan)
- Dutogliptin (being developed by Phenomix Corporation)
- Gemigliptin (being developed by LG Life Sciences)
- (Sitagliptin, Vildagliptin, Saxagliptin-are-approved-for-use-in-India) [6]

**Vildagliptin:**

It is a cyanopropilidine-based, orally bioavailable inhibitor of dipeptidyl peptidase 4 (DPP-4), with hypoglycemic activity. Vildagliptin Ciano moiety undergoes hydrolysis and this inactive metabolite is excreted mainly via the urine. Vildagliptin is an amino acid amide. Vildagliptin, previously identified as LAF237, is a new oral anti-hyperglycemic agent (anti-diabetic drug) of the new dipeptidyl peptidase-4 (DPP-4) inhibitor class of drugs. Vildagliptin subsequently acts by inhibiting the inactivation of glucagon -like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) by DPP-4. This inhibitory activity ultimately results in a two-fold action where GLP-1 and GIP are present to potentiate the secretion of insulin by beta cells and suppress glucagon secretion by alpha cells in the islets of Langerhans in the pancreas. Its IUPAC name is (2S)-1-[2-[(3-hydroxy-1-adamantyl) amino [acetyl] pyrrolidine-2-carbonitrile][7].

**Chemical structure of Vildagliptin**

**Dosage and administration:**

Vildagliptin was evaluated in a dose-response study by Ristic et al., assessing regimens of vildagliptin 25 mg twice daily, 25 mg daily, 50 mg daily, and 100 mg daily. Both vildagliptin 50- and 100-mg dosages led to significant reductions in HbA1c. Significant decreases in HbA1c, fasting plasma glucose levels, and prandial glucose levels were observed with doses of 25 mg twice daily. The highest vildagliptin dosage evaluated in the clinical trials was vildagliptin 100 mg twice daily in patients with type 2 diabetes mellitus; however, HbA1c values were not assessed for this dosage regimen. Because the labeling for vildagliptin is not yet FDA approved, dosage recommendations from the manufacturer are not available at this time. However, the drug’s pharmacokinetic properties allow for the possibility of once- or twice-daily dosing.[8]

**Mechanism of action:**

Vildagliptin inhibits dipeptidyl peptidase-4 (DPP-4). This in turn inhibits the inactivation of GLP-1 by DPP-4, allowing GLP-1 to potentiate the secretion of insulin in the beta cells. Dipeptidyl peptidase-4’s role in blood
glucose regulation is thought to be through degradation of GIP and the degradation of GLP-1[9].

**Current indications for use of vildi vigns:**
- First line in T2DM with HbA1c ≤7%. Second line as add-on therapy in T2DM patients already on 1 out of the following (metformin, SU, TZD, alpha-glucosidase inhibitor, miglitinide) for uncontrolled T2DM with HbA1c >7%. Third line as add-on therapy in T2DM patients already on combination therapy (2 out of the following (metformin, SU, TZD, alpha-glucosidase inhibitor, miglitinide).
- In patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance, as dual oral therapy in combination.
- Metformin, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin;
- Sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of a sulphonylurea and for whom metformin is inappropriate due to contraindications or intolerance;
- Thiazolidinedione, in patients with insufficient glycaemic control and for whom the use of a thiazolidinedione is appropriate;
- as triple oral therapy in combination with:
  - Sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.
  - Vildagliptin is also indicated for use in combination with insulin (with or without metformin) when diet and exercise plus a stable dose of insulin do not provide adequate glycaemic control[10].

**Pharmacokinetics:**
Upon oral administration vildagliptin is rapidly absorbed and is primarily eliminated by hydrolysis via multiple organs or tissues. It is metabolized by cytochrome P450(CYP)-mediated metabolic pathways with negligible protein binding [less than 10%] indicate yellow potential for drug interactions for vildagliptin. PK parameters of vildagliptin is not affected by age, gender, body mass index and food. Plasma half life is 2-4 hrs, the duration of action is 12-24 hrs. Major route of elimination is by hepatic metabolism. Nearly 20-25% dose reduction is needed in moderately severe liver and kidney disease patients[11].

**Pharmacodynamics:**
Vildagliptin belongs to a class of orally active antidiabetic drugs (DPP-4 inhibitors) that appear to have multiple functional benefits beyond simple blood-glucose control. One of these is a potential protective effect on pancreatic beta cells, which deteriorate in diabetes. Vildagliptin appears to be safe, very well tolerated, and efficacious. Following a meal, gut incretin hormones are released. The most important incretin hormones are GLP-1 and glucose-dependent insulinstropic polypeptide (GIP). The hormones secreted in the human small intestine are responsible for insulin release due to increased glucose levels. In contrast to agents that promote insulin secretion via glucose-independent mechanisms, GLP-1’s dependence on glucose concentration is considered beneficial due to a lower risk of hypoglycemia. GLP-1 also inhibits glucagon secretion and increases beta cell mass by stimulating proliferation and neogenesis. However, the clinical utility of GLP-1 is limited by its short half-life (2 minutes). GLP-1 is rapidly degraded by the proteolytic enzyme DPP-4. To enhance GLP-1 activity, inhibition of the DPP-4 enzyme is emerging as a novel therapeutic approach in the treatment of diabetes. Administration of vildagliptin enhances GLP-1’s ability to produce insulin in response to elevated concentrations of blood glucose, inhibit the release of glucagon following meals, slow the rate of gastric emptying and reduce food intake[12].

**Side effects:**
Asthenia, Dizziness, Gastro esophageal reflux disease, Headache, Hyperhidrosis, Tremors, Arthralgia, Constipation, Diarrhea, Flatulence, Hypoglycemia, Edema peripheral, Blister, Gastrointestinal disorder, Hepatitis, Pancreatitis, Nasopharyngitis, Angioedema, Edema, Upper respiratory tract infection, Antipathy, Weight increased, Malnutrition, Blood glucose decreased, Infestation[13].

**Contraindications:**
Contraindicated in patients with type 1 diabetes, diabetic ketoacidosis, severe liver impairment, during pregnancy and breast feeding. Caution should be exercised in patients with history of severe kidney disease. It may cause dizziness or fatigue, do not drive a car or operate machinery while taking this medication. Patient may develop with increased risk of foot ulcers and blistering of the skin; if it is so consult with your doctor. Monitor liver function and blood sugar level regularly while taking this medication[14].

**Safety and tolerability of vildagliptin:**
The introduction of vildagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, for the treatment of type 2 diabetes mellitus (T2DM) in 2007 provided clinicians with a novel and effective treatment option for lowering blood glucose, which neither caused weight gain nor increased the risk of hypoglycemia. Over the last decade, a vast panorama of evidence on the benefit–risk profile of vildagliptin has been generated in patients with type 2 diabetes mellitus. The overall safety and tolerability profile of vildagliptin was similar to placebo, and it was supported by real-world data in a broad population of patients with T2DM, making DPP-4 inhibitors, like vildagliptin, a safe option for managing patients with T2DM. A wealth of evidence from RCTs and real-world studies has consistently demonstrated that vildagliptin is an effective and well-tolerated treatment, with an established weight neutrality and low risk of hypoglycemia[15]. A pooled safety analysis of 58 trials has shown that the frequency of overall AEs, serious adverse events, discontinuations and deaths was similar between vildagliptin and all comparators. There was no specific trend in the AE and SAE profiles and the events were distributed across many different system organ classes (SOC). The four SOCs with highest incidence of AES were infections and infestations, gastrointestinal.
disorders, musculoskeletal and connective tissue disorders, nervous system disorders. Further evidence comes from a systematic review and meta-analysis, which concluded that vildagliptin is a safe therapeutic option for patients with T2DM, both as monotherapy and as add-on treatment. Vildagliptin is approved for use as monotherapy and in combination with other anti-hyperglycaemic agents. It is also indicated for special populations (elderly, renal impairment) and there are no contraindications beyond hypersensitivity to the active constituent. The key known risks include rare cases of mild to moderate elevations in hepatic enzymes, rare cases of angioedema (mostly in patients taking a concomitant ACE inhibitor) that resolved with ongoing treatment and acute pancreatitis, common for the GLP-1 based therapies. Vildagliptin continues to be a key treatment option for managing diverse patients with T2DM[16].

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