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Review on Teneligliptin: A novel antihyperglycemic agent

V. D. Gorde[1]* Dr. Punit R. Rachh[2]

[1] Research scholar, Department of pharmaceutical science, Bhagwant University, Ajmer, Rajasthan.

[2] Department of pharmaceutical science, Bhagwant University, Ajmer, Rajasthan.

ABSTRACT

Diabetes mellitus relates a metabolic disorder of collective aetiology which is characterized by chronic hyperglycaemia caused due to disturbances of carbohydrate, lipid and protein metabolism due to impaired β cell function of pancreas or insulin resistance or both. Dipeptidyl peptidase-4 (DPP-4) inhibitors have recently emerged as a new class of antidiabetic that show favorable results in improving glycemic control with a minimal risk of hypoglycemia and weight gain. Teneligliptin is a recently developed oral dipeptidyl peptidase 4 inhibitor indicated for the management of type 2 diabetes mellitus. Teneligliptin, characterized by a "J-shaped" structure formed by five consecutive rings which give unique binding characteristics, reflect in higher potency than other dipeptidyl peptidase 4 inhibitor. Teneligliptin is a novel antihyperglycemic agent with a preferable profile in terms of long-term efficacy and safety in patients with type 2 diabetes.

Keywords: Diabetes Mellitus, Dipeptidyl Peptidase 4 Inhibitor, Teneligliptin, Hypoglycemia,

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***Address for Correspondence:**

V. D. Gorde, Research scholar, Department of pharmaceutical science, Bhagwant University, Ajmer, Rajasthan.

Introduction:

Diabetes mellitus (DM) is probably one of the oldest diseases known to man. Diabetes is the increasingly growing metabolic threat of our contemporary era. Diabetes was first described in an Egyptian manuscript from 1500 BC, mentioning "too great emptying of the urine". Later on, Indian physicians described the disease and classified it as honey urine by the fact that ants were attacked by patient's urine. The term "diabetes" or "to pass through" was first used in 250 BC by the Greek Apollonius of Memphis[1]. There were more than 73 million cases of diabetes in India in 2017[2] and achieved undesired title 'centre for diabetes in world' with millions populations and many more rising[3].

Complications of diabetes are a major cause leading to morbidity and mortality in India and type 2 diabetes mellitus (T2DM) is thus considered as one of the major growing epidemics[4, 5]. Diabetes affects many organs, and complications due to high blood glucose are an important cause of disability, reduced quality of life, and premature death[6]. For the proper management of the disorder, the medicament has to be taken at regular intervals of time, lifelong. Conventional antidiabetic oral dosage forms offer no control over drug delivery, leading to fluctuations in plasma drug concentration and causes irregular glucose level in the patient's body. This shows that there are most requirements of the antidiabetic drugs to maintain the blood glucose level over the extended period of time for better therapeutic efficacy of drug.

Dipeptidyl peptidase-4 (DPP-4) inhibitors have recently emerged as a new class of antidiabetic that show favorable results in improving glycemic control with minimal risk Type 2 diabetes mellitus complications. Teneligliptin is a novel oral dipeptidyl peptidase-4 inhibitor for the treatment of type 2 diabetes mellitus (T2DM) having a unique structure characterized by five consecutive rings, which produce a potent and long-lasting effect[7].Teneligliptin is currently used in cases showing insufficient improvement in glycemic control even after diet control and exercise or a combination of diet control, exercise, and oral hypoglycemic drugs used include Biguanides, Sulphonylureas[8, 9].

Teneligliptin was originally synthesized by Mitsubishi Tanabe Pharma Corporation (Osaka, Japan) and was the first drug of its kind to be synthesized in Japan. Mitsubishi Tanabe Pharma Corporation and Daiichi Sankyo Co, Ltd, (Tokyo, Japan)

The economic costs of T2DM[10]

There is a substantial economic impact of diabetes on individuals, society, health care system, employer, and even the country in terms of loss of productivity. Reported

evidence suggests that there is a strong and direct economic impact of T2DM on the lives of people in lower income settings. In developing countries, where health care expenditure is many times out-of-pocket, an economic impact of T2DM is huge and may affect the long-term outcome of T2DM. There should be affordable medical treatment available to all. The cost of medicine should not be a barrier for health care. In this scenario, availability of economical DPP-4 inhibitors such as teneligliptin is a positive step.

Role of Teneligliptin in Type-2 Diabetes Mellitus therapy

Dipeptidyl peptidase-4 (DPP-4) work by increasing levels of active glucagon-like peptide-1 (GLP-1), thereby promoting insulin secretion, in a blood glucose-dependent manner, and hence decreasing glucose levels while minimizing the risk of hypoglycaemia. DPP-4 inhibitors are recommended in international guidelines[11]. Meta-analyses have suggested that DPP-4 inhibitors may be more potent in reducing HbA1c levels in Asian T2DM patients than in non-Asian patients[12,13]. Published evidence suggests that even 1% reduction in HbA1c reported significant reduction in the risk of long-term complications associated with T2DM[14].

Incretin hormones, namely glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released from enteroendocrine cells and enhance insulin secretion[15, 16]. Incretins are rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4), and have a very short half-life (t1/2) as a result. DPP-4 inhibitors increase the levels of active GLP-1 and GIP by inhibiting DPP-4 enzymatic activity; thus, in patients with diabetes, these inhibitors improve hyperglycemia in a glucose-dependent manner by increasing serum insulin levels and decreasing serum glucagon levels[15, 17,] Therefore, incretin-related agents such as DPP-4 inhibitors are promising drugs that can decrease glucose fluctuations in diabetic patients and have emerged as a new class of antidiabetic. Rise in new beta-cells and inhibition of their apoptosis is seen with Dipeptidyl peptidase-4 (DPP-4) which can potentially improve the disease pathogenesis. The American Diabetes Association (ADA) guidelines recommend Dipeptidyl peptidase-4 (DPP-4) as second-line therapy after metformin. Therefore, DPP-4 can be the choice of drugs in every T2D patient[18].

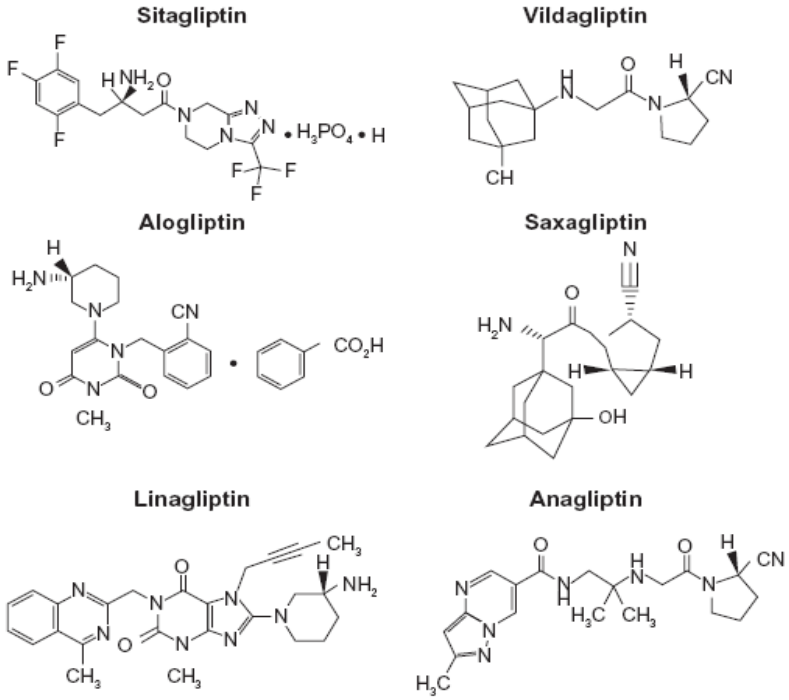

Figure 1: Structural heterogeneity of dipeptidyl peptidase-4 (DPP-4) inhibitors.

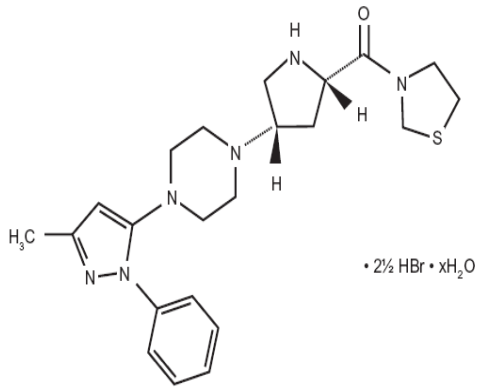

Figure 2: Chemical structure of teneligliptin.

Chemistry of Teneligliptin[19, 20]

Despite their common mechanism of action, DPP-4 inhibitors show marked structural heterogeneity (Figure 1). DPP-4 inhibitors may be classified into peptidomimetic (i.e., sitagliptin, vildagliptin, saxagliptin, and anagliptin) and non-peptidomimetic (i.e., alogliptin and linagliptin) subtypes. Teneligliptin, {(2S, 4S)-4-[4-(3-methyl-1-phenyl-1H-pyrazol-5-yl) piperazin-1-yl] pyrrolidin-2-yl} (1, 3-thiazolidin-3-yl) methanone hemipentahydrobromide hydrate exhibits a unique structure that is characterized by five consecutive rings (Figure 2) and is peptidomimetic. An X-ray co-crystal structure of teneligliptin with DPP-4 demonstrates that the key interaction occurs between the phenyl ring on the pyrazole and the S2 extensive subsite of DPP-4, which not only enhances the potency of the drug but also increases its selectivity.

Pharmacokinetic and pharmacodynamic properties of Teneligliptin[21]

The plasma concentrations of teneligliptin after the administration of teneligliptin at dosages of 10 or 20 mg once daily for 4 weeks revealed a median time to maximum concentration (Cmax) of 1.0 hour in both groups and a mean t1/2 of 20.8 and 18.9 hours, respectively. The maximum percentage of the inhibition in plasma DPP-4 activity was achieved within 2 hours after administration and was 81.3% and 89.7% in the 10 and 20 mg teneligliptin groups, respectively. A pharmacokinetic/pharmacodynamic study revealed that teneligliptin inhibits DPP IV activity over 24 hours, with elevation of activated glucagon-like peptide 1 (GLP-1) levels and the resulting suppression of postprandial hyperglycemia at all three daily meals. Monotherapy for 12 weeks significantly decreased hemoglobin A1c (HbA1c), fasting blood glucose, and 2-hour postprandial blood glucose levels in patients with type 2 diabetes. The therapeutic efficacy of teneligliptin over 52 weeks was confirmed not only as monotherapy but also as add-on therapy in patients with inadequately controlled blood glucose levels with sulfonylureas or thiazolidinediones.

Metabolism and excretion of Teneligliptin[22]

Teneligliptin has dual mode of excretion *i.e.,* hepatic and renal routes. About 34.4% of teneligliptin is excreted unchanged via the kidney and the remaining 65.6% teneligliptin is metabolized and eliminated via renal and hepatic excretion; 216 hours after the administration of 14C-labeled teneligliptin (20 mg), the cumulative excretion percentages of radioactive teneligliptin in urine and feces were 45.4% and 46.5%, respectively. Teneligliptin is eliminated via excretion with a half-life of 24.2 hours in human plasma from the kidney and metabolism involving certain enzymes.

Teneligliptin - Stronger DPP- 4 Inhibitor than other DPP- 4 Inhibitor[7, 22, 23]

Teneligliptin might have stronger inhibitory action against DPP-4 than other DPP- 4 inhibitors, because the plasma DPP-4 activity was significantly decreased after switching to teneligliptin. Teneligliptin has a unique structure, and binds to the S1, S2 and S2 extensive subsite of the DPP-4 enzyme, leading to enhanced potency and selectivity, and it is also a class 3 DPP-4 inhibitor. Additionally, binding of teneligliptin to the S2 extensive site, apartfrom the S1 and S2 sites, imparts stronger inhibitory action on the DPP-4 enzyme. Furthermore, teneligliptin was reported to have the J-shaped anchor-lock domain, strong covalent bonds with DPP-4 and more extensive S2 extensive binding, showing its higher inhibitory activity.

Table 1 Summary of the interactions of various DPP-4 inhibitors with DPP-4 enzyme[19, 22, 24, 25]

Class	DPP-4 inhibitors	Binding at DPP-4	Details
I	Vildagliptin and saxagliptin	S1 and S2 subsites	• Most fundamental level of interaction • Cyanopyrrolidine moieties bind with S1 • Hydroxy adamantly group binds with S2 • Saxagliptin has fivefold higher activity than vildagliptin
II	Alogliptin and linagliptin	S1, S2, S1′, and S2′ subsites	• Additional binding to S1′ and S2′ • Alogliptin binds to S1, S2, and S1′ • Linagliptin binds to S1, S2, S1′, and S2′ • Linagliptin had eightfold higher activity than alogliptin
III	Sitagliptin and teneligliptin	S1, S2, and S2 extensive subsites	• Binds S1, S2, and S2 extensive • Teneligliptin has fivefold higher activity than sitagliptin, because of: • Teneligliptin has favorable (J-shaped) structure leading to small loss of energy during binding with DPP-4 • Teneligliptin forms hydrogen bond with DPP-4 • Teneligliptin has more extensive binding at "S2 extensive" site than sitagliptin

A crystallographic study suggested that the key interaction between a phenyl ring on teneligliptin and the S2 extensive subsite of DPP-4 enhances the drug's potency and may increase its selectivity[12].Teneligliptin differs from other clinically used DPP-4 inhibitors, including sitagliptin, with regard to its elimination pathway. With teneligliptin, this involves both hepatic and renal excretion; whereas other DPP-4 inhibitors are typically eliminated by renal excretion only[13].This may reflect the potency of teneligliptin as an inhibitor of DPP-4, based on its unique binding characteristics derived from its chemical structure.

Teneligliptin in the Management of T2DM complications:

In adults, 20 mg of teneligliptin may be orally administered once daily. If this dosage is insufficient, the dosage is increased to 40 mg once daily.

Effect of Teneligliptin on blood glucose level[26, 27]

Treatment with dipeptidyl peptidase-4 (DPP-4) inhibitors, which are incretin-related antidiabetic agents, is widely accepted in clinical practice because of their low risk of hypoglycemiaand their beneficial effect on glucose control. To assess blood glucose control over 24 hours and the safety of teneligliptin at 10 and 20 mg doses, a randomized, double-blind, placebo-controlled, parallel-group study was conducted at four locations in Japan, results indicate that the once-daily administration of teneligliptin before breakfast improved blood glucose control, even at dinnertime.

Effect of Teneligliptin on insulin[7, 28]

Patients with T2DM receiving insulin therapy, with or without other antidiabetic agents, the addition of teneligliptin reported significant improvement in diurnal glycemic control and significant reductions in glucose fluctuations in 24-hour periods without increasing the risk of hypoglycaemia.

Effect of Teneligliptin on glucagon[7]

The postprandial glucagon levels significantly decreased after breakfast and lunch as well as after dinner in the teneligliptin-treated group compared with the corresponding values in the placebo group.

Renoprotection of Teneligliptin in type 2 diabetes patients with diabetic kidney disease[23, 29 -33]

Diabetic kidney disease (DKD), which is a diabetic vascular complication, is recognized as a major leading cause of end stage renal disease. Glucose control is fundamentally important for the prevention of DKD, as well as the control of blood pressure (BP) using renin–angiotensin system (RAS) inhibitors. However, hypoglycemia should be avoided, because hypoglycemia is closely related to increased mortality, which is associated with an increased incidence of cardiovascular disease. In addition to their glucose-lowering effect, DPP-4 inhibitors have renoprotective effects, which are mainly a reduction in albuminuria, independent of the glucose-lowering effect. Teneligliptin has strong and long DPP-4 inhibitory effects, and no dose adjustment may be required, even if the patient has renal function decline. Because 34.4% of the administered dose of teneligliptin is excreted unchanged through the renal route, whereas 65.6% is metabolized and eliminated through the hepatic and renal routes. In addition, the distribution of teneligliptin to the kidney is high because of its lipophilicity, possibly showing a renoprotective effect. DPP-4 inhibitors exerted their renoprotective effect through anti-inflammation, antioxidativeStress and anti-fibrosis.

Effects of Teneligliptin on lipid profiles[34 - 38]

The lipid profile is an important determinant of cardiovascular risk in type 2 diabetes. It can affect antidiabetic therapy and is important in the clinical management of patients with type 2 diabetes. A potential beneficial effect of DPP-4 inhibitors on cholesterol, which could contribute to a reduction in cardiovascular risk. The administration of several DPP-4 inhibitors reduces post-prandial triglyceride levels in humans, mice, and hamsters.

Gliptins in combination with other oral antidiabetic agents[39 - 42]

Since DPP-4 inhibitors and metformin improve glycemic control via different, albeit potentially complementary, mechanisms, combination therapy with these two agents should provide effective and potentially additive glycemic control. Studies using combination therapy of DPP-4 inhibitors and metformin (as one pill) showed favorable results in glycemic control because of favorable pharmacokinetic characteristics and complementary pharmacodynamic effects, which include enhanced incretin effect, suppressed hepatic glucose production, and improved peripheral insulin sensitivity. Moreover, in general, the combination of this drug into a single tablet improves patients' compliance and often results in a lower cost of treatment.

Teneligliptin protects against hypoxia/reoxygenation-induced endothelialcell injury[43 - 46]

Cardiovascular complications are the main causes of mortality in diabetic patients. Teneligliptin is a newly developed anti-diabetic agent. It has been reported that teneligliptin has a vascular protective capacity in preclinical studies and diabetes patient. The prevalence of diabetes mellitus has been a major threat to human health worldwide. The high prevalence of diabetes has increased the risk of serious diabetes-related complications. Diabetesassociated vascular diseases affect nearly all blood vessel types and sizes including arteries, veins and microvasculature. The long-time burden of diabetes often causes cardiovascular complications and ultimately, cardiovascular disease. Epidemiological data have shown that patients with type 2 diabetes mellitus have a considerable two to four fold higher risk of cardiovascular morbidity and mortality as compared with the non-diabetes population. It has been recognized that vascular complications are the cause of most morbidities, hospitalizations, and mortalities in diabetes patients. Curing cardiovascular complications and lowering glucose are the goals for an effective treatment for type 2 diabetes. Gliptins are a class of glucose-lowering agents for the treatment of type 2 diabetes. Recently, several kinds of gliptins have been shown to be effective in improving endothelial function, reducing oxidative and pro-inflammatory states, and exerting beneficial effects on cardiovascular function. Teneligliptin is one of the newly approved gliptins and has been shown be effective in treating type 2 diabetes. Interestingly, teneligliptin has displayed various cellular effects that are associated with vascular protection. It has been shown that teneligliptin can improve cardiac remodeling in hypertensive rats and improve endothelial dysfunction in prediabetic rats. A recent study demonstrated that teneligliptin inhibits atherogenesis in mice. In human subjects, administration of teneligliptin in diabetes patients improves patients' endothelial function and heart function. Teneligliptin also regulates platelet-derived microparticles, suggesting that it possesses an anti-atherothrombotic effect

in patients with type 2 diabetes. Taken together, teneligliptin appears to be a very appealing anti-diabetic agent with the potent dual effects of reducing glucose and vascular protection. This versatile functional profile indicates that teneligliptin is a very promising drug for the control of diabetes as well as its vascular complications.

The neurovascular protective effect of gliptin in murine MCAO modeland brain endothelial cells[47, 48]

Gliptinsare a novel class of treatment agents for diabetes, and recent studies have linked the use of gliptins to neuroprotection.Recently, studies have suggested that administrationof gliptins could exert neuroprotective effects in mice.A meta-analysis that included more than 9000 human subjects concluded that gliptins may have certain protective effects in stroke condition.

DPP-4 Inhibitors and Patient Weight[49 - 52]

Studies on the influence of DPP-4 inhibitors on patient weight demonstrated variable results but are generally considered to be neutral.

The Novel Dipeptidyl Peptidase-4 Inhibitor Teneligliptin Prevents High-Fat Diet-Induced Obesity Accompanied With Increased Energy Expenditure in Mice[53]

Dipeptidyl peptidase-4 (DPP-4)-deficient mice exhibit prevention of obesity with increased energy expenditure. The novel DPP-4 inhibitor teneligliptin prevents obesity and obesity-related manifestations with increased energy expenditure.

Conclusion

All major guidelines recommend metformin as thefirst-line treatment in patients with diabetes. The American Diabetes Association (ADA) guidelines recommend dipeptidyl peptidase-4 as second-line therapy after metformin. Therefore, dipeptidyl peptidase-4 can be the choice of drugs in every T2D patient. Despite their common mechanism of action, DPP-4 inhibitors show marked structural, Pharmacokinetic and pharmacodynamic heterogeneity. Teneligliptin differs from other clinically used DPP-4 inhibitors. Teneligliptin has a unique structure and binding site leading to enhanced potency and selectivity, imparts stronger inhibitory action on the DPP-4 enzyme.

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