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Teneligliptin: A Review on Therapeutic Role in Diabetics Mellitus

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Abstract: Diabetes challenges the global population, diabetic organizations across the globe call for unanimous resonance of *Diabetes Voice* to tackle diabetes with healthy living. With the discovery of new pathophysiology associated with diabetes, patients are gaining access to the newer therapeutic classes. Teneligliptin is a dipeptidyl peptidase-4 inhibitor, is indicated for the treatment of adults with type 2 diabetes (T2DM). It acts like an insulin/ glucagonmodulator controlling blood glucose over 24 hours. It is effective in tackling short-term glycemic fluctuations and improvement in β-cell parameters is observed soon after treatment. Half-life of 26.9 hours ensures once a day administration. This article reviews on clinical particulars, pharmacology, and therapeutic efficacy and tolerance of teneligliptin in the treatment of adults with T2DM.In patients with type 2 diabetics, treatment with teneligliptin produced clinically significant improvements in hemoglobin A1C, fasting plasma glucose (FPG) and 2-hour post-prandial glucose (PPG) compared to placebo. Teneligliptin, as a Dipeptidyl Peptidase-4 Inhibitor improves early-phase insulin secretion with Type 2 Diabetes and additionally its pleiotropic benefits of Cardio protection.A comprehensive comparison of Teneligliptin with other gliptins in the class & provides a concise summary of all clinical trials till the date with Teneligliptin monotherapy & combination with other ant-diabetic drugs.
Keywords : Teneligliptin, Pleiotropic benefits,Early-phase, Monotherapy.

Introduction

Diabetes mellitus is a chronic condition prevalent worldwide. It is estimated that more than 246 million individuals have diabetes, with this number expected to increase to 366 million by the year 2030.Around 193 million, close to half of the people with diabetes, are unaware of their disease. The chronic hyperglycemia of diabetes is associated with long term damage to various organs, including the eyes, kidneys, nervous system, heart, and vasculature. India has a long history regarding the epidemiology of diabetes. In an effort to optimize glycemic control and also to reduce the burden of diabetic complications, several classes of oral hypoglycemic agents have been developed. Inadequate glycemic control results in microvascular & macrovascular complications such as cardiovascular diseases, peripheral arterial disease, retinopathy, nephropathy & neuropathy. From a simple disease of insulin deficiency, to a bifactoral model of insulin deficiency & resistance, to a multifactorial condition, diabetes is a challenging proposition [2].

Over the years as the understanding of diabetes pathophysiology has evolved, there has been a tremendous improvement in the way we approach & manage this disease [3]. The triumvirate of impaired

insulin secretion, increased hepatic glucose production & decreased peripheral glucose utilization has always remained the core defects responsible for the development & progression of type2 diabetes. However, as diabetic research has evolved, the gut (gastrointestinal tissues) has emerged as anadd-on affiliate that contributes to pathogenesis of type 2 diabetes. Intestinal secretion of insulin or incretins namely, glucagon-like peptide (GLP-1) & glucose-dependent insulinotropic polypeptide (GIP) governs blood glucose homeostasis. They stimulate insulin biosynthesis & enhance insulin secretion from β-cell of pancreas.GLP-1 and not GIP additionally suppresses glucagon secretion from α-cell of pancreas thereby reducing hepatic glucose output [4]. GLP-1 being α/β cell modulator has evolved as a successful drug target. Following release, incretin hormones are rapidly inactivated by dipeptidyl peptidase-4 (DPP-4) enzyme. This has opened up avenues for treatment strategies targeting intestinal secretion of insulin or incretins. Apart from being insulin/glucagon modulators, they do not cause hypoglycemia or weight gain, and clinical studies have shown capability for improvement in β-cell function [5]. These classes differentiate themselves from traditional anti-diabetic agents dueto their β-cell preservationcapabilities which could be linked to slow the progression of type 2 diabetes. GLP-1 agonists, e.g. exenatide are to be administered subcutaneously while DPP-4 inhibitors, e.g. gliptins are administered orally. Additionally, GLP-1 agonists are associated with high incidences of nausea [6]. All these factors make DPP-4 inhibitors potentially the better candidate for combination therapy with other anti-diabetic drugs.Teneligliptin is a third generation DPP-4 inhibitor approved for treatment of type 2 diabetes. It is currently available in Japan, South Korea, Argentina and India. It is under pre-registration in Indonesia & under Phase I trials in US & Phase II trials in Denmark, Germany, Hungary, Lithuania, Poland, Romania & UK.

Pharmacodynamics of Teneligliptin

Teneligliptin has a unique chemical structure amongst currently available DPP-4 inhibitors consisting of five consecutive rings, whereas other DPP-4 inhibitors have a peptidomimetic (i.e. saxagliptin, sitagliptin, vildagliptin and anagliptin) or non-peptidomimetic (i.e. alogliptin and linagliptin) structure [5, 6].DPP-4 enzyme has several binding sites namely S_1, S_2, S_1', S_2' & S_2 extensive subunit as shown in **Figure 1**. An interaction of DPP-4 inhibitors with S_1& S_2 is considered to be the fundamental interaction required for DPP-4 interaction. Additional interaction with S_1', S_2' & S_2 extensive site may further increase the DPP-4 inhibition. DPP-4 inhibitors are classified according to their interactions with DPP-4 enzymes. DPP-4 inhibitors are classified as Class 1, Class 2 and Class 3 based on their interaction at DPP-4 sub sites. Class 1 inhibitors (Vildagliptin & Saxagliptin) bind to S_1& S_2 and are considered as fundamental/basic inhibitors. Class 2 (Alogliptin & Linagliptin) bind to additional site of S_1, S_2 & S_1' and may produce more DPP-4 inhibition than Class 1, Linagliptin additionally binds to the S_2' sub site. Class 3 inhibitors (Sitagliptin & Teneligliptin) binds to S_1, S_2& additional site of S_2 extensive and produce more extensive DPP-4 inhibition [7].

Teneligliptin consists of a considerably rigid "J-shaped" structure formed by five rings, four of which are directly connected to DPP-4 which provides strongest binding to DPP-4 enzymes as compared to other gliptins (**Figure 2**).

Figure 1. DPP-4 enzyme with binding sites.

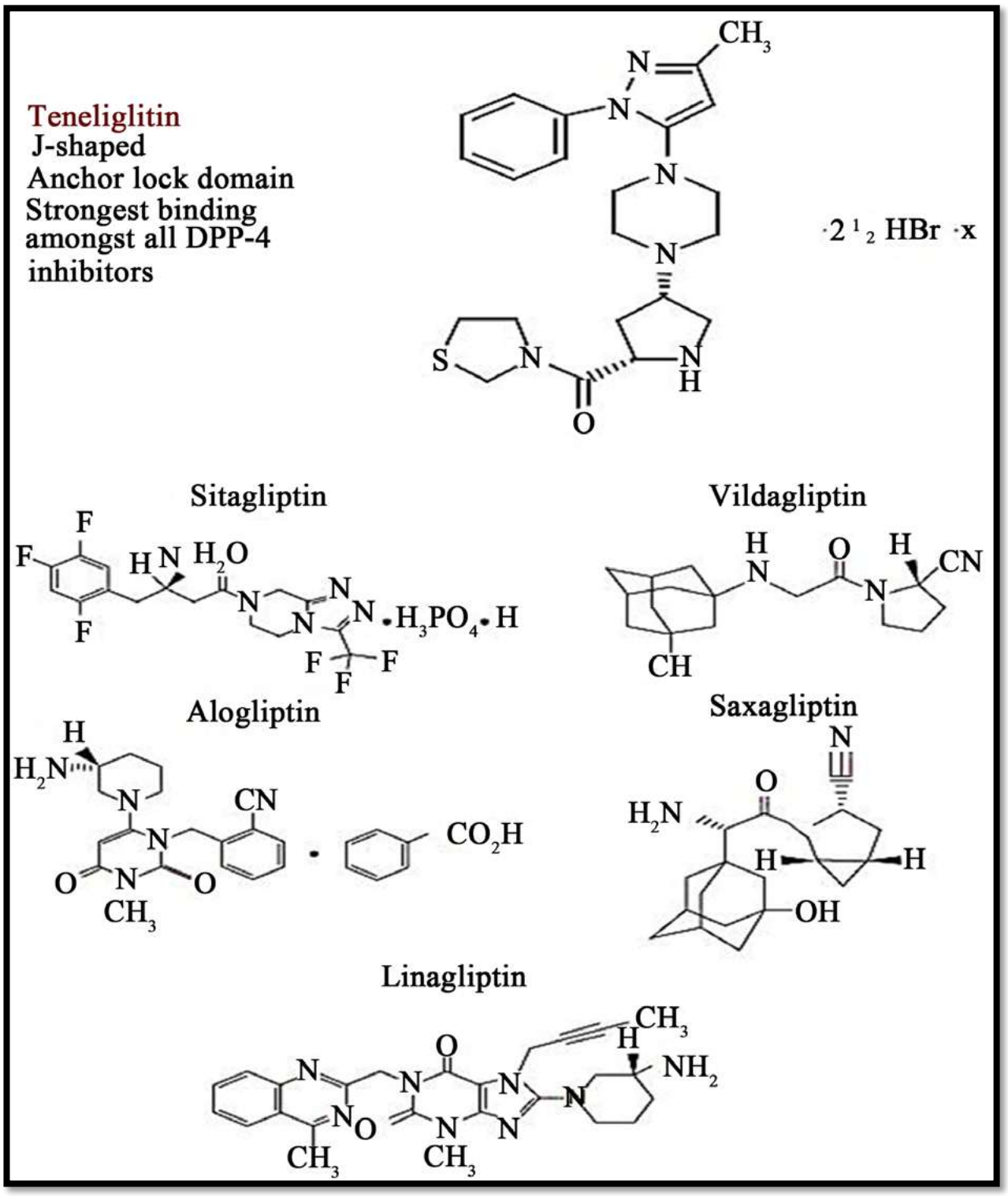


Figure 2:Summary of chemical structure of various gliptins

In in vitro and in vivo studies, teneligliptin exhibited competitive, highly selective, potent and long lasting inhibition of human and recombinant DPP-4 [5, 7, and 8].

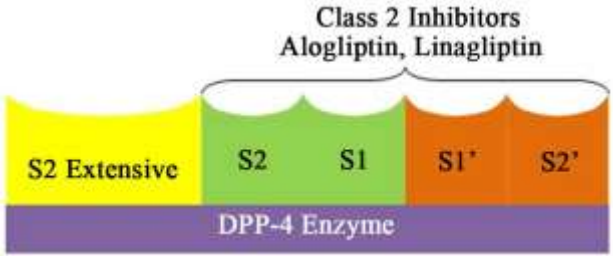
Table 1. Summary of the interactions of various DPP-4 inhibitors with DPP-4 enzymes

Vildagliptin &

Saxagliptin

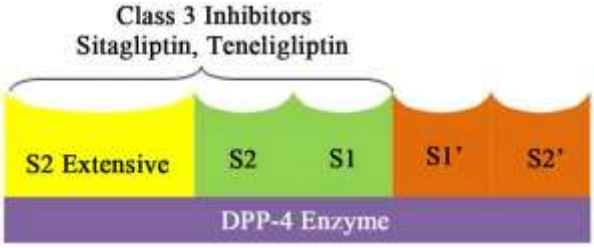
Alogliptin

& Linagliptin



Sitagliptin

& Teneligliptin



For Teneligliptin, introduction of the "anchor lock domain", which binds to the S2 extensive sub site, increased the activity by 1500-fold over the corresponding fragment that binds to S1 & S2 only. Although, Teneligliptin &Sitagliptin both fall in Class 3 & both bind to S2 extensive subunit, Teneligliptin has 5-fold higher activity than Sitagliptin for DPP-4 enzymes. Teneligliptin has total contact area of 2.08 nm2 while Sitagliptin has total contact area of 1.90 nm2. Teneligliptin may bind more tightly to the S2 extensive sub site as a result of stronger hydrophobic interactions mediated by the "anchor lock domain". Binding of the anchor lock domain may relate to the residence time of DPP-4 inhibition and the long in vivo duration of action [7].Inhibition of the DPP-4 substrateby Teneligliptin occurs in a manner that involves formation of a reversible covalent enzyme–inhibitor complex.This complex binds and dissociates from the catalytic site of the DPP-4 substrate very slowly resulting in persistentDPP-4 inhibition even after the drug is inactivated. This means that the catalytic activity remains inhibited of human and recombinant DPP-4 even after the free drug has been cleared from the circulation. Binding to the S2 extensive sub site, DPP-4inhibitors can increase not only their inhibitory activity but also their selectivity towards other DPP enzymes.

The J-shape and anchor-lock domain, contributes to the strong inhibitory function and potency of this drug withthe lowest IC50 value (0.37 nmol/L). It is extremely selective for DPP-4 as compared toDPP-8 (703 fold) & DPP-9 (1460 fold).

The plasma concentrations of Teneligliptin after administration of dosages 10 or 20 mg once daily for 4 weeksrevealed a median time to maximum concentration (Cmax) of 1.0 hour with both dosages respectively. The maximumpercentage of the inhibition in plasma DPP-4 activity was achieved within 2 hours after administrationand was 81.3% and 89.7% with Teneligliptin 10 and 20 mg, respectively [10]. The percentage inhibition ofDPP-4 activity at 24 hrs, after administration was 53.1% in Teneligliptin 10 mg group & 61.8% in Teneligliptin20 mg group. The active plasma GLP-1 concentration was higher after Teneligliptin administration than placebothroughout the day, even at 24 hours after administration. The AUC0-2h values for the active GLP-1 concentrationafter breakfast, lunch and dinner were 8.0, 8.4 and 7.8 pmol·h/L respectively, in Teneligliptin 10 mg groupand 8.3, 7.9, and 8.6 pmol·h/L respectively, in Teneligliptin 20 mg group [10]. As compared to Teneligliptin 10mg group, increase in AUC0-2h for active GLP-1 concentration was slightly greater after dinner

in Teneligliptin 20 mg group. Differences in the AUC0-2h for the active GLP-1 concentration between both the Teneligliptin treated groups and the placebo group were statistically significant ($p < 0.001$).

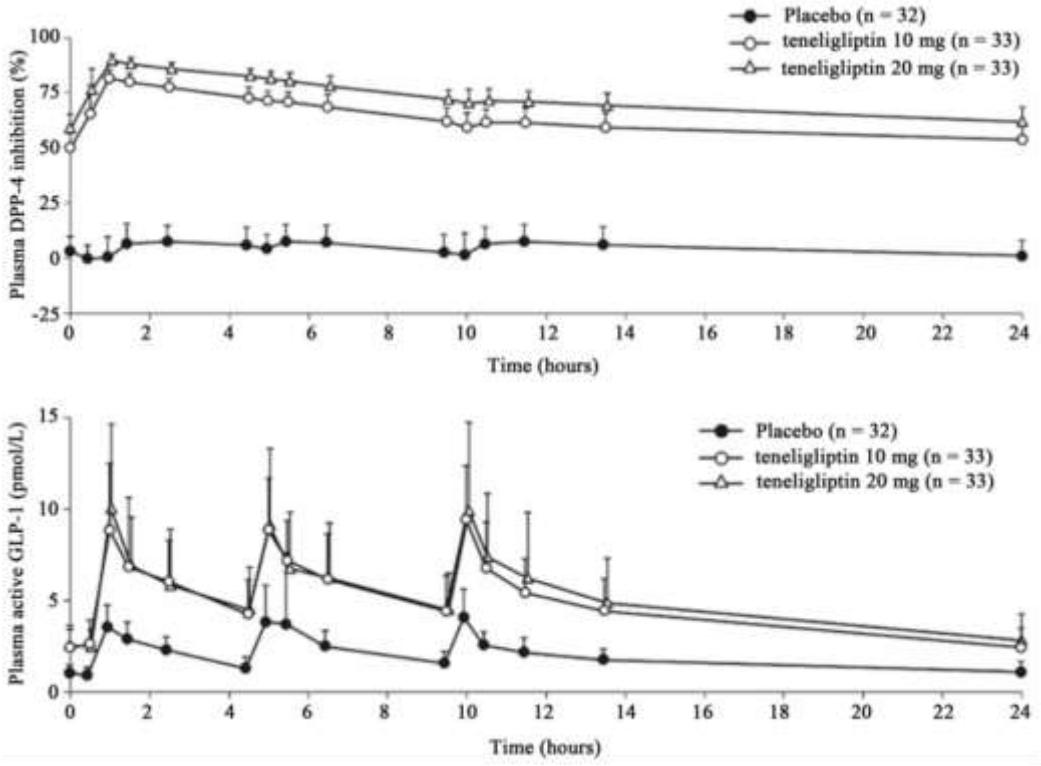


Figure 3: The percentage inhibition of plasma DPP-4 activity and plasma active GLP-1 concentrations in Teneligliptin 10mg & 20 mg groups as compared to placebo are shown.

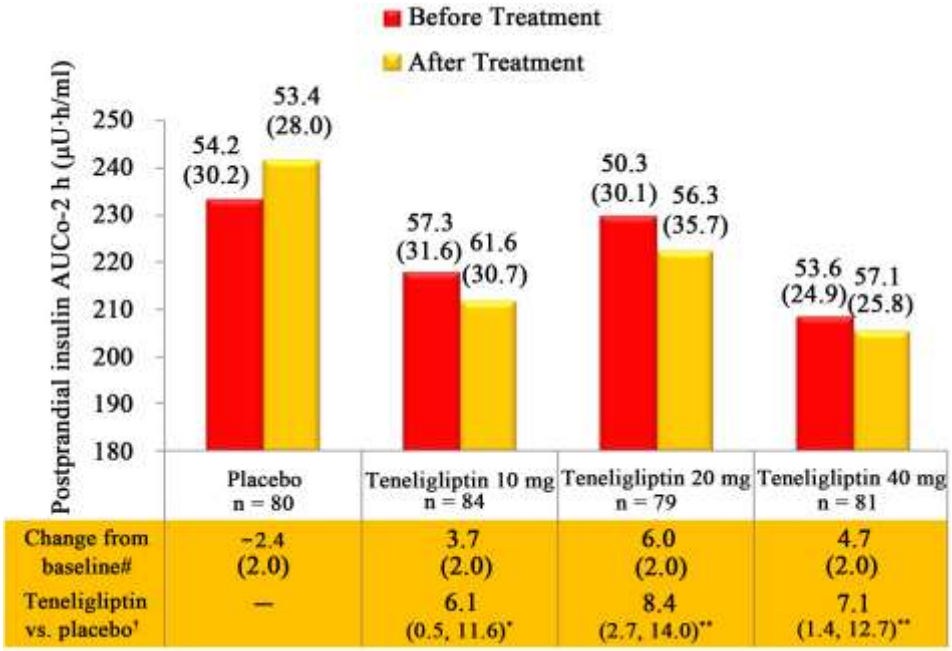


Figure 4:Postprandial insulin AUC0-2h after administration of Teneligliptin 10mg, 20 mg, 40 mg vs placebo. AUC0-2h areaunder the curve from 0 to 2 h after standard meal. ANCOVA was performed using treatment group as the fixed factor andbaseline value as a covariate. *p < 0.05; **p < 0.01 vs placebo.

Pharmacokinetic of Teneligliptin

Teneligliptin is rapidly absorbed in healthy volunteers after a single radiolabeled 20 mg dose, with maximum plasma concentrations attained in 1.33 hr [26]. The drug is 78% - 80% bound to plasma proteins [27]. An overview of Teneligliptin pharmacokinetics is mentioned in

In humans, teneligliptin is primarily metabolized by cytochrome P450 (CYP) 3A4 and flavin mono oxygenases (FMO) 1 and 3 to several metabolites of unknown biological activity [4, 15]. A thiazolidine-1-oxide derivative (designated M1) is the most abundant metabolite and accountsfor 14.7 % of the AUC total radioactivity after a single 20 mg radiolabelled dose of teneligliptin [11]. At least 90 % of the radiolabelled dose was excreted within 216 h, with 45.4 % excreted in the urine and 46.

Using a physiologically based population pharmacokinetic model, which included in vitro studies and human data from healthy volunteers and clinical studies, there were no clinically relevant effects on the pharmacokinetics of teneligliptin based on age or ethnicity (Caucasians, Japanese and Chinese ethnicity) [12]. In patients with mild (Child-Pugh score 5–6) or moderate (Child-Pugh score 7–9) hepatic impairment, there were no clinically relevant effects on the pharmacokinetics of teneligliptin [4, 20]. There is no reported clinical experience in patients with severe hepatic impairment (Child-Pugh score [9; Sect. 6) [4]. There were no clinically relevant effects on the pharmacokinetics of teneligliptin in patients with renal impairment [4].

Pleiotropic Benefits of Teneligliptin

Improvement in Endothelial Function

Daily blood glucose fluctuations have been shown to cause oxidative stress and induce inflammatory markers leading to endothelial dysfunction and arteriosclerosis. There is also evidence that the postprandial glycemic state contributes to atherosclerotic risk [13]. Teneligliptin appears to have potent, sustained effects on glycemic control, which are beneficial in ameliorating the effects of hypoglycemia and postprandial hyperglycemia on the development of diabetes complications [14]. Takehiro Hashikata et al. [15] evaluated the effects of teneligliptin on left ventricular function in 29 type 2 diabetic patients for 3 months.

Improvement was seen not only in LV function (LV ejection fraction, 62.0% ± 6.5% to 64.5% ± 5.0%; $p = 0.01$; peak early diastolic velocity/basal septal diastolic velocity (E/e) ratio, 13.3 ± 4.1 to 11.9 ± 3.3; $p = 0.01$) but also in endothelial function (reactive hyperemia peripheral arterial tonometry [RHPAT] index; 1.58 ± 0.47 to 2.01 ± 0.72; $p < 0.01$).

Adiponectin is an adipocyte-derived hormone that plays an important role in the regulation of insulin sensitivity & energy homeostasis. In metabolic disorder like obesity, there is decrease in adiponectin levels in adipocytes. Adiponectin receptor is involved in regulating glucose uptake promotion & fatty acid oxidation. Enhanced adiponectin levels, in turn, increases protection against inflammation, insulin resistance & cardiovascular disorders. Circulating adiponectin levels increased (27.0 ± 38.5 pg/mL to 42.7 ± 33.2 pg/mL; $p < 0.01$) without changes in patient body weight after treatment with Teneligliptin.

- Improvement in Lipid Profile
- Natriuretic & Diuretic Effects of Teneligliptin
- Weight Neutral
- Improvement in Endothelial Function

- **Improvement in Lipid Profile**

Pharmacokinetic profile	**Teneligliptin**	**Sitagliptin**	**Vildagliptin**	**Linagliptin**
Route	Oral	Oral	Oral	Oral
Bioavailability	63% - 85%	87%	85%	30%
T_{max}	1.33 h	1 to 4 h	1.75 h	1.5 h
Effect of food	No	No	No	No
Protein Binding	78% - 80%	38%	9.3%	70% - 80%
Metabolites	Inactive	Inactive	Inactive	Inactive

Drug-Drug interactions	No majorclinically Relevantdrug-druginteractions	Plasma AUC of digoxin was increased by 11%, otherwise no major interaction reported	Low potential for drug interaction	Rifampin

- **Natriuretic & Diuretic Effects of Teneligliptin**

GLP-1R & DPP-4 are expressed in the renal proximal tubular brush border, where they regulate Na+ reabsorption [16]. DPP-4 exist in physical complexes with Na+-H+ exchanger isoform NHE3 in the brush border membranesof renal proximal tubule cells. The NHE3-DPP-4 complex exists predominantly in the microvilli of renaltubules [17]. DPP-4 inhibition reduces NHE3 activity and consequently induces natriuretic [18]. In addition tothis, GLP-1 activation induces diuresis. DPP-4 inhibitors are ant diabetic agents that have diuretic & natriuretic effects, which might contribute in reducing blood pressure. A major proportion of diabetic patients are often diagnosed with hypertension. Furthermore, DPP-4 inhibitors have recently been shown to enhance nitric oxide release in hypertensive or diabetic models [38]-[40]. Thus, the action of DPP-4 inhibitors might be favorable for diabetic patients with hypertension. DPP-4 converts intact B-type natriuretic peptide [BNP (1 - 32)] into its des-SerPro form [BNP (3 - 32)] [41]. Diuretic & natriuretic effects of BNP (3 - 32) are less than those of BNP (1- 32). The relative increase of BNP (1 - 32) because of DPP-4 inhibitors might therefore be effective on dieresis &natriuretic. Masao Moroi et al. [42] investigated diuretic & natriuretic effects of Teneligliptin & whether these were associated with the stimulation of GLP-1R in rats. The study concluded that Teneligliptin (10 mg/kg)had diuretic and natriuretic effects with a reduction of plasma DPP-4 activity over 6 hours. The natriuretic effectof Teneligliptin was inhibited by the GLP-1R antagonist, exendin 9 - 39, whereas thediuresis was not affected.

These results suggest that the mechanism of natriuretic was different from that of diuresis, and the natriuretic is associated with the stimulation of GLP-1R.

- **Weight Neutral**

DPP-4 inhibitors are generally considered to be weight neutral [43]-[45]. In a Phase III trial, 20 mg of Teneligliptinwas administered to 151 patients with type 2 diabetes, who were previously treated with diet control andexercise treatment alone. The dose of Teneligliptin was increased to 40 mg in patients with HbA1c levels greaterthan 7.3% at any time after week 24. The mean body weight change of the patients at week 52 (mean ± SD) was+0.18 ± 2.14 kg ($p = 0.3254$), which indicated that the effect of Teneligliptin on body weight was neutral [10].

- **Current Status of Teneligliptin in Type 2 Diabetes**

The progressive nature of T2DM, although its management initially focuses on lifestyle changes (i.e. improved diet and exercise), it invariably requires pharmacological intervention with at least one antidiabeticmedication (typically with metformin monotherapy orcombination therapy depending upon HbA1c levels) [28,29]. The increasing availability of various classes of antidiabetic drugs that have differing and complementarymechanisms of action and/or different safety profiles andpropensities for drug-drug interactions, has facilitatedoptimization of the management of the disease on anindividual patient basis.

Current guidelines recommend atarget HbA1c level of \7 % [28] or B6.5 % [29] isachieved, although in certain individuals HbA1c levelshigher or lower than these may be appropriate [28, 29].In addition to targeting glycemic control, antidiabeticdrugs should ideally aim to minimize the risk of adverseoutcomes such as bodyweight gain and hypoglycaemia,both of which are considered cardiovascular risk factors[28]. As a class, the efficacy of DPP-4 inhibitors is wellestablished, with these agents having a convenient oncedailyoral regimen and bodyweight neutral effects, andassociated with a low risk of hypoglycaemia (hypoglycaemia neutral) [28, 29].

In the absence of direct head-to-headclinical trials, the position of teneligliptin in themanagement of T2DM relative to other classes of antidiabeticagents and other DPP-4 inhibitors remains to bedetermined. In 12- or 16-week, placebo-controlled trialsteneligliptin 20 or 40 mg once daily (typically 20 mg/day),as monotherapy (Sect. 4.1) or in combination with metformin,glimepiride or pioglitazone (Sect. 4.2), improvedglycemic control, including in patients with ESRD (Sect.4.4) and was generally well tolerated (Sect. 5). MostTEAEs were of mild intensity and relatively few patientsdiscontinued treatment because of these events. Improvements in glycemic control observed in short-term trialswere maintained at 52 weeks in extension phases of thesetrials and in 52-week interventional studies (Sect. 4.3), with no new safety concerns identified during this period (Sect.5). Thus, teneligliptin is a useful option for the treatment ofadults with T2DM who have not responded adequately totreatment with diet and exercise, or the addition ofantidiabetic drugs.

❖ **Improves Early-Phase Insulin Secretion in Drug-Naı¨ve Patientswith Type 2 Diabetes**

Once-daily teneligliptin improved glycemic control in Japanese patients with T2D. Twelve weeks of teneligliptintreatment clearly improved IGI30min and the AUC120minSUIT index in drug naive Japanese patients with T2D. TheOGTT may be a useful method for estimating insulin secretion per se in patients with T2D receiving DPP-4inhibitors.

Some investigation is done in changes of insulin secretion before and after 12 weeks treatment with a DPP-4 inhibitor,teneligliptin, in drug naive patients with T2D withlow insulinogenic index (IGI) determined by an oral glucose tolerance test. IGI [30-min insulin - 0-mininsulin)/ (30-min glucose - 0-min glucose) = IGI30min] and AUC120min for secretoryunits of islets in transplantation index {C-peptide (ng/mL) 9 1500/ [PG (mg/dL) - 61.7] = SUIT index) was measured.It is found that the twelve weeks of teneligliptin treatment markedly improved b-cell function in drug naive Japanese patients with T2D.

There is no severe hypoglycemia or major side effects occurred.

References

1. Cho, N.H., Whiting, D., Forouhi, N., Guariguata, L., Hambleton, I., Li, R., Majeed, A., Mbanya, J.C., Montoya, P.A.,Motala, A., Narayan, V., Ramachandran, A., Rathmann, W., Roglic, G., Shaw, J., Silink, M. and Zhang, P. (2015) IDFDiabetes Atlas. 7th Edition, International Diabetes Federation, Karakas Print, Brussels, 1-144.
2. Kalra, S., Das, A.K. and Sahay, R. (2013) Managing Diabetes: The Drivers of Change. Journal of Social Health &Diabetes, 1, 3-5. http://dx.doi.org/10.4103/2321-0656.109827
3. Kalra, S. (2013) Recent Advances in Pathophysiology of Diabetes: Beyond the Dirty Dozen. Journal of Pakistan MedicalAssociation, 2, 277-280.
4. Baetta, R. and Corsini, A. (2011) Pharmacology of Dipeptidyl Peptidase-4 Inhibitors. Drugs, 71, 1441-1467.http://dx.doi.org/10.2165/11591400-000000000-00000
5. Drucker, D.J. and Nauck, M.A. (2006) The Incretin System: Glucagon Like Peptide-1 Receptor Agonists & DipeptidylPeptidase-4 Inhibitors in Type 2 Diabetes. The Lancet, 368, 1696-1705.http://dx.doi.org/10.1016/S0140-6736(06)69705-5
6. Verspohl, E.J. (2009) Novel Therapeutics for Type 2 Diabetes: Incretin Hormone Mimetics (Glucagon-Like Peptide-1Receptor Agonists) and Dipeptidyl Peptidase-4 Inhibitors. Pharmacology & Therapeutics, 124, 113-138.http://dx.doi.org/10.1016/j.pharmthera.2009.06.002
7. Nabeno, M., Akahoshi, F., Kishida, H., Miyaguchi, I., Tanaka, Y., Ishii, S. and Kadowaki, T. (2013) A ComparativeStudy of the Binding Modes of Recently Launched Dipeptidyl Peptidase IV Inhibitors in the Active Site. Biochemicaland Biophysical Research Communications, 434,191-196. http://dx.doi.org/10.1016/j.bbrc.2013.03.010\
8. Kushwaha, R.N., Haq, W. and Katti, S.B. (2014) Discovery of 17 Gliptins in 17-Years of Research for the Treatmentof Type 2 Diabetes: A Synthetic Overview. Chemistry & Biology Interface, 4, 137-162.
9. Röhrborn, D., Wronkowitz, N. and Eckel, J. (2015) DPP4 in Diabetes. *Frontiers in Immunology*, **6**, 1-20.http://dx.doi.org/10.3389/fimmu.2015.00386
10. Kishimoto, M. (2013) Teneligliptin: A DPP-4 Inhibitor for the Treatment of Type 2 Diabetes. Diabetes, MetabolicSyndrome and Obesity: Targets and Therapy, 6, 187-195. http://dx.doi.org/ 10.2147/DMSO.S35682

11. Suh, S. and Kim, J.H. (2015) Glycemic Variability: How Do We Measure It and Why Is It Important? Diabetes & MetabolismJournal, 39, 273-282. http://dx.doi.org/10.4093/dmj.2015.39.4.273
12. Dąbrowska, A.M., Tarach, J.S. and Kurowska, M. (2012) 1,5-Anhydroglucitol (1,5-AG) and Its Usefulness in ClinicalPractice. Medical and Biological Sciences, 26, 11-17. http://dx.doi.org/10.2478 /v10251-012-0049-z
13. Ceriello, A. (2000) The Post-Prandial State and Cardiovascular Disease: Relevance to Diabetes Mellitus. Diabetes/Metabolism Research and Reviews, 16,125132.http://dx.doi.org/10.1002/ (SICI)15207560(200003/04)16:2<125::AID-DMRR90>3.0.CO;2-4
14. Morishita, R. and Nakagami, H. (2015) Teneligliptin: Expectations for Its Pleiotropic Action. Expert Opinion onPharmacotherapy, 16, 417-426
15. Hashikata, T., Yamaoka-Tojo, M., Kakizaki, R., Nemoto, T., Fujiyoshi, K., Namba, S., Kitasato, L., Hashimoto, T.,Kameda, R., Maekawa, E., Shimohama, T., Tojo, T. and Ako, J. (2015) Teneligliptin Improves Left Ventricular DiastolicFunction and Endothelial Function in Patients with Diabetes. Heart Vessels, 8.http://dx.doi.org/10.1007/s00380-015-0724-7
16. Von Websky, K., Reichetzeder, C. and Hocher, B. (2014) Physiology and Pathophysiology of Incretins in the Kidney.Current Opinion in Nephrology and Hypertension,23,54-60http://dx.doi.org/10.1097/ 01.mnh.0000437542.77175.a0
17. Girardi, A.C., Degray, B.C., Nagy, T., Biemesderfer, D. and Aronson, P. (2001) Association of Na+-H+ Exchanger Isoform NHE3 and Dipeptidyl Peptidase IV in the Renal Proximal Tubule. The JournalofBiologicalChemistry,276,46671-46677.http://dx.doi.org/10.1074/jbc.M106897200
18. Girardi, A.C., Knauf, F., Demuth, H.U. and Aronson, P.S. (2004) Role of Dipeptidyl Peptidase IV in Regulating Activityof Na+/H+ Exchanger Isoform NHE3 in Proximal Tubule Cells. The American Journal of Physiology—Cell Physiology,287, C1238-C1245.http://dx.doi.org/10.1152/ ajpcell.00186.2004

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