

Teneligliptin: a review on cardio-renal safety**Dixit K. Patel¹, Ramandeep T. Sharma¹, Himanshu A. Patel², Hanmant V. Barkate^{1*}**¹Department of Medical services, Intas pharmaceuticals Ltd, Ahmedabad, Gujarat, India,²Department of Nephrology, Zydus Hospital, Ahmedabad, Gujarat India**Received:** 20 February 2016**Accepted:** 29 February 2016***Correspondence to:**Dr. Hanmant V. Barkate,
Email: drbarkate@intaspharma.com**Copyright:** © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.**ABSTRACT**

Type 2 diabetes mellitus (T2DM) is a well-known risk factor for cardiovascular disease and chronic kidney disease (CKD). Various drugs including DPP4 inhibitors with different pharmacologic profile are being used in patients with type 2 diabetes for improving glycaemic control. Cardiovascular (CV) safety is one of the important aspects while selecting the glucose lowering therapies. In addition, DPP-4 inhibitors differ in their mode of excretion and degree of accumulation, which require dose/frequency modification in patients with impaired renal function. Therefore, understanding the cardio-renal safety profile of DPP4 inhibitors is of great importance. Teneligliptin is a DPP4 inhibitor, approved recently for the management of type 2 diabetes mellitus. The purpose of the present review is to integrate published literature and evaluate the cardio-renal safety of teneligliptin in type 2 diabetic patients. As per the available evidence, teneligliptin has apparently positive effects on CV safety markers like no QT prolongation at clinically relevant dose, small but significant improvement in left ventricular (LV) function, improvement in adiponectin levels and improvement in endothelial dysfunction. These findings support the cardiovascular safety of teneligliptin in T2DM patients. Dual route of excretion makes teneligliptin suitable (no dose adjustment required) for T2DM patients with renal failure. Available clinical evidence suggests that teneligliptin exerts cardiovascular safety in T2DM patients. This drug can be used in T2DM patients with CKD including end stage renal disease patients without any major safety concern.

Keywords: Teneligliptin, Dipeptidyl peptidase-4 (DPP4) inhibitors, cardiovascular safety, Renal safety, Type 2 diabetes mellitus**INTRODUCTION****Background**

Diabetes is one of the leading global health issues of the 21st century. Currently 415 million adults have diabetes worldwide.¹ Type 2 diabetes mellitus (T2DM) is a well-known risk factor for cardiovascular disease and chronic kidney disease (CKD).² People with T2DM have an elevated risk of CVD compared with those without T2DM and a poorer prognosis following an adverse CV event.^{3,4} Glycaemic control provides only limited achievement in reducing the macrovascular complications associated with T2DM.⁵ There have been persistent concerns about potential adverse cardiovascular effects of sulfonylureas as well as with few DPP4 inhibitors. Hence, selecting the optimal

therapy for individuals with T2DM requires cautious consideration regarding CV safety of glucose lowering therapies. In 2008, the US Food and Drug Administration (FDA) responded to this need by issuing guidelines that mandate a thorough assessment of CV risk in glucose-lowering drugs.⁶ The standards of diabetes care recommend that optimisation of glycaemic control results in reduction in the risk or slowing the progression of CKD. However, pharmacokinetics of the drugs available to control hyperglycaemia are affected by kidney function and should therefore be either avoided or used at reduced doses in patients with CKD.⁷ Therefore, understanding the cardio-renal safety profile of Teneligliptin (newer DPP4 inhibitor) is of paramount importance.

Teneligliptin, a DPP4 inhibitor, was approved for the management of type 2 diabetes mellitus in Japan (2012),⁸ in South Korea (2014) and in India (2015).⁹ In addition to effective glycaemic control, results of various clinical trials also suggested that teneligliptin, as monotherapy or add-on therapy was generally well tolerated in patients with T2DM. The purpose of the present review is to integrate published literature and contemporary evaluation of the cardio-renal safety of teneligliptin in type 2 diabetic patients.

Concerns with DPP4 inhibitors

Apart from glucose-lowering effect, DPP4 inhibitors have a diverse impact on cardiovascular system. This impact is due to presence of GLP-1 receptors in human cardiac myocytes which is well documented since last two decades.¹⁰ The point of concern is the rate of hospitalization for heart failure, which was increased by 27% with saxagliptin in SAVOR-TIMI 53 trial.¹¹ A recently published EXAMINE trial also pointed out that the rate of heart failure was increased in patients on alogliptin.¹² Moreover vildagliptin use may enhance the risk of angioedema in patients taking ACE inhibitors. The cardiovascular (CV) effects may be due to the fact that DPP4 inhibitors have multiple targets, leading to undesirable effects with the inhibition of various substrates.¹³

Patients with type 2 diabetes mellitus frequently develop renal function impairment. DPP-4 inhibitors vary in their mode of excretion due to their different pharmacokinetic profile in patients with impaired kidney function should therefore be either avoided or a dose adjustment should be done in diabetic patients with CKD.¹⁴

Evidence acquisition

A literature search was carried out from various established sources like abstracts or full text publications of the indexed journal for this review. The official clinical trial registry at www.clinicaltrials.gov was also searched to identify future/on-going long-term CV outcomes clinical trials with incretin-based therapies in individuals with T2DM. Appropriate articles were selected for review and discussion in light of the author's knowledge.

Teneligliptin: cardiovascular effect

Teneligliptin: LV function

One of the most primordial preclinical manifestation of diabetic cardiomyopathy is LV diastolic dysfunction.¹⁵ Various studies have been reported that GLP-1 improves left ventricular function in ischemic heart disease condition in animal as well as in human.^{16,17} Hashikata T. et al have conducted single-centre 3 month follow up study in 27 T2DM patients for 3 month with teneligliptin. The results of the study suggested that there were

significant improvements in left ventricular (LV) systolic and diastolic function from baseline (LV ejection fraction, 62.0±6.5% to 64.5±5.0%, p=0.01). Improvement in endothelial function was also significant, RH-PAT (reactive hyperaemia peripheral arterial tonometry) index was also significantly improved (1.58±0.47 to 2.01±0.72, p<0.01). Furthermore, there was significant increment in circulating adiponectin levels without change in body weight (27.0±38.5 pg/ml to 42.7±33.2 pg/ml, p<0.01). Improvements in LV function, adiponectin levels and endothelial dysfunction support the cardiovascular safety of teneligliptin in T2DM patients.¹⁸

Teneligliptin has been used in various clinical trials either as a monotherapy^{14,19,20} or with metformin,²¹ glimeperide,²² pioglitazone²³ or insulin²⁴ in duration ranging from 4 weeks to 1 year. None of these trials have reported any drug related cardiovascular adverse effect.

Teneligliptin: QT interval

QT interval in the ECG is a measure of cardiac repolarisation. An increased QT interval is a risk factor for arrhythmias and sudden cardiac death. Hence, any drug that increases the QT interval may increase the risk of CV events.²⁵ Sitagliptin,²⁶ saxagliptin,²⁷ linagliptin²⁸ and vildagliptin²⁹ are not associated with QT interval prolongation at clinically relevant concentrations in healthy individuals.

A randomized, double-blind, placebo and moxifloxacin-controlled, parallel-group comparative study was conducted in 240 healthy adult male and female subjects to investigate the effect of multiple-dose administration of teneligliptin (40, 160 mg) on QTc intervals. Placebo, teneligliptin 40 mg, and 160 mg were administered orally once daily for 4 days (placebo group, 40 mg group and 160 mg group). In the moxifloxacin group (positive control group), placebo was administered orally once daily for 3 days and moxifloxacin 400 mg on day 4. QTc interval prolongation was observed only time points near t_{max} after administration of teneligliptin 160 mg because few patients had comorbid arrhythmia or ischemic heart diseases. No clinically significant QTc interval prolongation was observed at 40 mg. The study suggested that teneligliptin was not associated with QT interval prolongation at clinically relevant dose (maximum recommended dose 40 mg) in healthy individuals.³⁰ However teneligliptin should be used with caution when co-administered with drugs known for QT prolongation like class IA or class III antiarrhythmic drugs.³¹

Teneligliptin: long-term effects on CVD

Trials for long term effects on CVD of DPP4 inhibitors like sitagliptin (TECOS trial), saxagliptin (SAVOR-TIMI 53 trial) and alogliptin (EXAMINE trial) have been recently published. Similarly TOPLEVEL (Teneligliptin on the progressive left ventricular diastolic dysfunction with Type 2 diabetes mellitus study) trial has been

designed to assess long term cardio vascular effect of teneligliptin. It will be an interventional, randomized, single blind clinical trial, to assess the cardiac diastolic function of long term treatment with teneligliptin compared to that without teneligliptin in approximately 1000 patients with type 2 diabetes mellitus by two arms; one arm will include patients showing E/e' by echocardiography less than 8, the other arm will include patients showing E/e' by echocardiography more than 8. The results of this trial will evaluate the long term effect of teneligliptin on deaths by cardiovascular events, all-cause mortality, rate of hospitalization by cardiovascular events, rate hospitalization due progression of heart failure, change of the left ventricular mass index, change of plasma levels of NT-proBNP etc. The trial is expected to be completed in June 2019.³²

Teneligliptin: renal safety

Dose adjustment of DPP-4 inhibitors in patients with chronic kidney disease

T2DM is a well-documented risk factor for nephropathy and chronic kidney disease (CKD) and is the most common cause of end-stage renal disease (ESRD) during haemodialysis. However, most of the available oral antidiabetic drugs (OAD) are affected by kidney function and should therefore be either avoided or require a dose/frequency adjustment in diabetic patients with CKD.⁷

DPP-4 inhibitors differ in their mode of excretion and degree of accumulation in patients with impaired renal function. At present, total seven DPP-4 inhibitors-sitagliptin, saxagliptin, vildagliptin, alogliptin, linagliptin, teneligliptin, and anagliptin are available in different countries. All of them except linagliptin (5 mg) and teneligliptin (20 mg) require dose adjustment in T2DM patients with CKD depending on their eGFR level hence, these five agents of the class are available in lower strength or recommended with reduced frequency to prevent drug accumulation.³³ The main excretion pathways, dialyzability and recommended dose adjustment for available DPP-4 inhibitors in CKD or patients on haemodialysis are shown in Table 1.

Table 1: Recommended dose adjustment for dipeptidyl peptidase 4 inhibitors in patients with chronic kidney disease.

DPP-4 inhibitors	GFR (ml/min)		
	Up to 50 (ml/min)	50-30 (ml/min)	<30 (ml/min)
Sitagliptin	100 mg	50 mg	25 mg
Alogliptin	25 mg	12.5 mg	6.25 mg
Vildagliptin	100 mg	50 mg	
Saxagliptin	5 mg	2.5 mg	
Anagliptin	200 mg		100 mg
Linagliptin	5 mg		
Teneligliptin	20 mg		

DPP-4 = Dipeptidyl peptidase-4; GFR = glomerular filtration rate.

Conventional doses of sitagliptin (100 mg daily) and alogliptin (25 mg daily) should be reduced to 50 and 12.5 mg daily, respectively, when CrCl is between 30 and 50 ml/min and reduced further to 25 and 6.25 mg daily when it is <30 ml/min. For vildagliptin and saxagliptin, a half of the conventional doses is required for CrCl <50 ml/min. For anagliptin, a 100 mg daily is recommended for CrCl <30 ml/min. Dialyzability of sitagliptin, alogliptin, vildagliptin, saxagliptin and teneligliptin is 3.5-13.5%, 7.2%, 3%, 23%, 15.6% respectively. Dialyzability for anagliptin is not known and linagliptin is unlikely to be dialyzed.³³ Here, we describe the pharmacokinetic, clinical efficacy and safety of teneligliptin in patients with CKD, including those receiving dialysis.

Teneligliptin: pharmacokinetics in subjects with renal impairment

In humans, teneligliptin is primarily metabolized by cytochrome P450 (CYP) 3A4 and flavin monooxygenases (FMO).³⁴ At least 90% of the radiolabeled dose was excreted within 216 hour, with 45.4% excreted in the urine and 46.5% excreted in the faeces. Approximately 21% of teneligliptin is excreted in the urine as unchanged drug.³⁴ Therefore no dose adjustment is required for teneligliptin at any stage of renal failure because of dual route of excretion (hepatic & renal).

An independent study was undertaken to determine the pharmacokinetics of an estimated therapeutic dose of 20 mg teneligliptin in subjects with renal impairment and ESRD. Administration of teneligliptin at 20 mg in patients with renal impairment showed no significant changes in half-life or in maximum concentration (C_{max}) corresponding to the level of renal impairment. Compared with healthy adult subjects, the $AUC_{0-\infty}$ of patients with mild renal impairment ($50 \leq$ creatinine clearance [Ccr] & ≤ 80 ml/min), moderate renal impairment ($30 \leq$ Ccr & < 50 ml/min) and severe renal impairment (Ccr < 30 ml/minute) was roughly 1.25 times, 1.68 times, and 1.49 fold higher than that of healthy adult subjects, respectively. In addition, the AUC_{0-43h} of patients with ESRD was approximately 1.16 times higher than that of healthy adult subjects.³⁵ Additionally, 15.6% of teneligliptin was eliminated via haemodialysis. Linagliptin is one of the most preferred DPP4 inhibitor in diabetic patients with renal impairment patients and above results are comparable with the similar study of linagliptin (Table 2). The data suggest that renal impairment has a negligible effect on teneligliptin pharmacokinetics, increase in exposure was not affected by the stages of renal impairment or ESRD and was less than two fold when compared with that in healthy subjects. These results suggest that dose adjustment might not be needed for teneligliptin in patients with any stage of renal impairment or ESRD.

Table 2: Accumulation of linagliptin and teneligliptin in subjects with renal impairment or ESRD compared with healthy subject (Indirect comparison).

Renal impairment (RI)	AUC _{0-t} * value with reference to healthy volunteer	
	Linagliptin (5mg) ³⁶ (n=6 in each group)	Teneligliptin (20mg) ³⁵ (n=8 in each group)
Mild (eGFR >50 to ≤80)	1.29 fold	1.22 fold
Moderate (eGFR >30 to ≤50)	1.56 fold	1.56 fold
Severe (eGFR ≤30)	1.41 fold	1.49 fold
ESRD (≤30+dialysis)	1.54 fold	0.97 fold (Before HD), 1.16 fold (after HD)

*t=24 hr for linagliptin, 72 hrs for teneligliptin

Efficacy and tolerability of teneligliptin in patients with CKD

Otsuki H et al³⁷ had conducted prospective study to assess the safety and efficacy of teneligliptin for diabetic patients undergoing hemodialysis. Patients were switched from existing antidiabetic therapy to teneligliptin 20 mg once daily (n=14). Patients who continued with their existing antidiabetic therapy (n=29) were enrolled in control group. Average HbA1c level was 6.4% at baseline and 4.8 years was mean duration of haemodialysis treatment. There was a significant (p<0.05) improvement in mean HbA1c levels at week 8, 16 and 24 from baseline in patients who switched to teneligliptin treatment. There was no significant difference in mean HbA1c between the teneligliptin and control group at 24 weeks (p=0.057). The other parameters like mean glucose level and glycated albumin were also significantly (p<0.05) improved from baseline in teneligliptin group. The study concluded that teneligliptin 20 mg is safe, well tolerated and efficacious in diabetic patients with end-stage renal disease.

CONCLUSION

In addition to effective glycaemic control, results of various clinical trials suggested that teneligliptin, as monotherapy or add-on therapy was generally well tolerated in patients with T2DM. It has apparently positive effects on CV safety markers like no clinically meaningful QT prolongation, small but significant improvement in LV function, improvement in adiponectin levels and improvement in endothelial dysfunction. However the impending results from TOPLEVEL trial will provide a perspective on long term impact of teneligliptin on various parameters of the CV

outcome including the incidence of heart failure. Dual route of excretion makes teneligliptin suitable for T2DM patients with renal failure and results of pharmacokinetic study also suggests that renal impairment has a negligible effect on teneligliptin pharmacokinetics/accumulation. Additionally, teneligliptin has been found to be safe, well tolerated and efficacious in diabetic patients with end-stage renal disease. Current clinical evidences suggest that teneligliptin ensures cardiovascular safety in T2DM patients. This drug can be used in T2DM patients with CKD including end stage renal disease patients without any major safety concern.

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Conflict of interest: Dr. Dixit Patel, Dr. Ramandeep Sharma & Dr. Hanmant Barkate are salaried employees of Intas Pharmaceuticals Ltd., Ahmedabad, Gujarat, India.

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