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Teneligliptin in Type 2 Diabetes Mellitus: A Comprehensive Review

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Abstract: *Type 2 diabetes mellitus (T2DM) represents a global health challenge characterized by progressive βcell dysfunction and insulin resistance. Dipeptidyl peptidase-4 (DPP-4) inhibitors have emerged as an important therapeutic class for managing T2DM by enhancing incretin hormone activity. Teneligliptin, a novel DPP-4 inhibitor with unique structural features, offers distinct pharmacological advantages including prolonged half-life, minimal renal excretion, and sustained enzyme inhibition. This comprehensive review examines the molecular pharmacology, clinical efficacy, safety profile, and therapeutic positioning of teneligliptin in contemporary diabetes management. Evidence from randomized controlled trials demonstrates that teneligliptin effectively reduces glycated hemoglobin (HbA1c) levels, improves postprandial glucose control, and exhibits favorable tolerability with low hypoglycemia risk. The drug's unique pharmacokinetic profile allows for flexible dosing in patients with renal or hepatic impairment, addressing an important unmet need in special populations. This review synthesizes current evidence on teneligliptin's mechanism of action, comparative effectiveness, cardiovascular safety, and place in therapy, providing clinicians with a comprehensive understanding of this therapeutic option for individualized T2DM management.*

Keywords: Teneligliptin, Type 2 Diabetes Mellitus, DPP-4 inhibitor, Incretin therapy, Glycemic control, Antidiabetic agents

I. INTRODUCTION

1.1 Epidemiology and Burden of Type 2 Diabetes Mellitus

Type 2 diabetes mellitus has reached epidemic proportions globally, with the International Diabetes Federation estimating that approximately 537 million adults aged 20-79 years were living with diabetes in 2021, projected to rise to 783 million by 2045. The prevalence continues to increase across all regions, driven by aging populations, urbanization, dietary changes, and sedentary lifestyles (Saeedi et al., 2019). T2DM accounts for approximately 90-95% of all diabetes cases and is associated with substantial morbidity, mortality, and economic burden due to microvascular and macrovascular complications including retinopathy, nephropathy, neuropathy, cardiovascular disease, and stroke (Zheng et al., 2018).

The pathophysiology of T2DM is characterized by two primary defects: progressive pancreatic β-cell dysfunction leading to inadequate insulin secretion, and peripheral insulin resistance primarily in skeletal muscle, liver, and adipose tissue. Additionally, incretin deficiency or resistance contributes significantly to the dysregulation of glucose homeostasis (DeFronzo et al., 2015). The progressive nature of T2DM necessitates treatment intensification over time, with many patients eventually requiring combination therapy to achieve and maintain glycemic targets. Current therapeutic approaches aim not only to reduce hyperglycemia but also to minimize hypoglycemia risk, prevent weight gain, preserve β-cell function, and reduce cardiovascular risk (American Diabetes Association, 2023).

1.2 The Incretin System and DPP-4 Inhibition

The incretin effect refers to the phenomenon whereby oral glucose administration elicits a greater insulin response compared to intravenous glucose administration at equivalent plasma glucose concentrations. This effect is mediated primarily by two gut-derived incretin hormones: glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic

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polypeptide (GIP) (Nauck et al., 2016). These hormones are secreted from intestinal L-cells and K-cells, respectively, in response to nutrient ingestion and enhance glucose-stimulated insulin secretion from pancreatic β-cells, suppress inappropriate glucagon secretion from α-cells, slow gastric emptying, and promote satiety (Drucker, 2018).

In individuals with T2DM, the incretin effect is substantially diminished, contributing to postprandial hyperglycemia and impaired glucose homeostasis. Both GLP-1 and GIP are rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4), which cleaves the N-terminal dipeptide from these hormones, rendering them inactive within minutes of secretion (Deacon, 2019). DPP-4 is a serine exopeptidase expressed ubiquitously in various tissues including the kidney, liver, intestine, and vascular endothelium, existing both as a membrane-bound form and in soluble form in plasma. The recognition that DPP-4 rapidly inactivates incretin hormones led to the development of DPP-4 inhibitors as a therapeutic strategy to enhance endogenous incretin activity and improve glucosedependent insulin secretion (Mulvihill& Drucker, 2014).

DPP-4 inhibitors, also known as gliptins, represent a class of oral antidiabetic agents that work by competitively and selectively inhibiting the DPP-4 enzyme, thereby prolonging the action of endogenous GLP-1 and GIP. This mechanism results in enhanced glucose-dependent insulin secretion, suppression of glucagon secretion, and improvement in both fasting and postprandial glucose levels without increasing the risk of hypoglycemia or causing weight gain (Scheen, 2018). Since the approval of the first DPP-4 inhibitor sitagliptin in 2006, several agents in this class have been developed, including vildagliptin, saxagliptin, linagliptin, alogliptin, and teneligliptin, each with distinct pharmacological characteristics.

1.3 Introduction to Teneligliptin

Teneligliptin (3-[(2S,4S)-4-[4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-yl]-1,3thiazolidin-4-one hydrobromide hydrate) is a third-generation DPP-4 inhibitor developed by Mitsubishi Tanabe Pharma Corporation and approved for the treatment of T2DM in Japan in 2012, followed by several other Asian countries including India, South Korea, and Indonesia (Kishimoto, 2013). Teneligliptin possesses unique structural features that distinguish it from other DPP-4 inhibitors, including five consecutive rings in its chemical structure that contribute to its potent and sustained enzyme inhibition profile.

The development of teneligliptin was driven by the goal of creating a DPP-4 inhibitor with enhanced pharmacological properties, including potent and long-lasting enzyme inhibition, minimal renal elimination to allow use in patients with renal impairment without dose adjustment, and favorable safety and tolerability profiles (Kishimoto, 2013). Preclinical studies demonstrated that teneligliptin exhibits potent DPP-4 inhibitory activity with an IC50 value of 0.74 nmol/L and high selectivity for DPP-4 over related enzymes such as DPP-8, DPP-9, and other serine proteases (Yoshida et al., 2012). The drug's unique pharmacokinetic profile, characterized by multiple elimination pathways and prolonged enzyme inhibition exceeding 24 hours at therapeutic doses, positions it as a distinctive option within the DPP-4 inhibitor class.

This comprehensive review aims to provide an in-depth analysis of teneligliptin's pharmacological properties, clinical efficacy, safety profile, and therapeutic role in the management of T2DM, synthesizing evidence from preclinical studies, clinical trials, real-world studies, and comparative effectiveness research.

II. MOLECULAR PHARMACOLOGY AND MECHANISM OF ACTION

2.1 Chemical Structure and Molecular Properties

Teneligliptin has the molecular formula C22H30N6OS•HBr•2.5H2O and a molecular weight of 568.51 (including the hydrobromide hydrate). Its chemical structure features a unique pentacyclic ring system comprising a thiazolidinone ring, pyrrolidine ring, piperazine ring, and a 3-methyl-1-phenyl-1Hpyrazole moiety (Kishimoto, 2013). This complex ring structure is responsible for the drug's tight binding to the DPP-4 active site and contributes to its prolonged duration of action. The presence of the thiazolidinone ring is a distinctive structural feature not shared by other marketed DPP-4 inhibitors and may contribute to its unique binding characteristics and pharmacological profile.

The stereochemistry of teneligliptin is precisely defined, with (2S,4S) configuration at the pyrrolidine ring, which is critical for optimal binding to the DPP-4 enzyme active site. Crystallographic studies have revealed that teneligliptin

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binds to DPP-4 through multiple interactions including hydrogen bonding, hydrophobic interactions, and aromatic stacking, resulting in a stable enzyme-inhibitor complex (Yoshida et al., 2012). The compound exhibits high lipophilicity with a calculated logP value conducive to cellular membrane permeability and tissue distribution.

2.2 DPP-4 Enzyme Structure and Inhibition Mechanism

Dipeptidyl peptidase-4 is a 766-amino acid glycoprotein that exists as a homodimer, with each monomer consisting of an α/β-hydrolase domain containing the catalytic site and an eight-bladed βpropeller domain. The catalytic triad comprises Ser630, His740, and Asp708 residues, which execute the peptidase activity through a classical serine protease mechanism (Rasmussen et al., 2003). DPP-4 specifically cleaves dipeptides from the N-terminus of peptides containing proline or alanine in the penultimate position, which includes the incretin hormones GLP-1 and GIP among many other substrates.

Teneligliptin functions as a competitive, reversible inhibitor of DPP-4, binding non-covalently to the enzyme's active site and preventing substrate access. The inhibitor binds within the S1 and S2 subsites of the DPP-4 active site, with the pyrrolidine ring occupying the S1 pocket and forming key interactions with Glu205 and Glu206, while the extended ring system occupies the S2 pocket and establishes hydrophobic contacts with residues including Tyr547, Trp629, and Tyr666 (Yoshida et al., 2012). The unique five-ring structure enables multiple points of contact with the enzyme, contributing to the high binding affinity and slow dissociation rate.

Kinetic studies demonstrate that teneligliptin exhibits competitive inhibition with respect to substrate, with a Ki (inhibition constant) of approximately 0.56 nmol/L. The inhibitor displays a slow off-rate from the enzyme (koff), resulting in prolonged occupancy of the active site even after plasma drug concentrations decline (Kishimoto, 2013). This slow dissociation kinetics, characterized by a residence time exceeding 24 hours at therapeutic concentrations, contributes to the sustained pharmacodynamic effect and allows for once-daily dosing.

2.3 Selectivity Profile and Off-Target Effects

Selectivity for DPP-4 over related peptidases is crucial to minimize potential off-target effects. Teneligliptin demonstrates high selectivity for DPP-4 with minimal inhibitory activity against closely related enzymes including DPP-8 (IC50 >100 μmol/L), DPP-9 (IC50 >100 μmol/L), fibroblast activation protein (FAP), prolyl oligopeptidase (POP), and other serine proteases (Yoshida et al., 2012). The selectivity ratio (IC50 for DPP-8 or DPP-9/IC50 for DPP-4) exceeds 100,000-fold, indicating an excellent therapeutic window. This high selectivity is important because DPP-8 and DPP-9 are ubiquitously expressed intracellular enzymes with roles in immune function and cell biology, and their inhibition has been associated with toxicity in preclinical studies.

Comprehensive off-target profiling against a panel of 150 receptors, ion channels, enzymes, and transporters revealed no significant interactions at concentrations up to 10 μmol/L, indicating minimal potential for unintended pharmacological effects (Kishimoto, 2013). This favorable selectivity profile contributes to teneligliptin's good tolerability and low risk of drug-related adverse events.

2.4 Effects on Incretin Hormones and Glucose Homeostasis

By inhibiting DPP-4, teneligliptin increases the circulating concentrations and half-lives of active GLP-1 and GIP, amplifying their physiological effects on glucose homeostasis. Administration of teneligliptin results in 2- to 3-fold increases in postprandial active GLP-1 levels and similar elevations in active GIP levels (Kishimoto, 2013). These elevated incretin levels enhance glucose-dependent insulin secretion from pancreatic β-cells through activation of GLP-1 receptors and GIP receptors, which are G-protein coupled receptors that stimulate adenylyl cyclase, increase intracellular cAMP, and trigger insulin granule exocytosis.

The glucose-dependent nature of incretin-mediated insulin secretion is a key safety feature, as insulin release is stimulated only when blood glucose levels are elevated, thereby minimizing hypoglycemia risk. Concurrently, teneligliptin-mediated incretin enhancement suppresses glucagon secretion from pancreatic α-cells in a glucose-dependent manner, reducing hepatic glucose production and contributing to improved fasting glucose levels (Kishimoto, 2013). In addition to these direct effects on islet hormone secretion, incretin hormones exert additional

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beneficial effects including slowed gastric emptying, which reduces the rate of glucose absorption and attenuates postprandial glucose excursions, and enhanced satiety, which may contribute to modest weight stabilization or reduction.

Preclinical studies in diabetic animal models have demonstrated that teneligliptin administration improves glucose tolerance, reduces fasting and postprandial glucose levels, enhances insulin secretion, and reduces glucagon levels (Yoshida et al., 2012). Long-term studies in db/db mice showed that chronic teneligliptin treatment preserved pancreatic β-cell mass and improved islet morphology, suggesting potential disease-modifying effects beyond acute glycemic control, although such effects remain to be definitively established in humans.

III. PHARMACOKINETICS AND PHARMACODYNAMICS

3.1 Absorption and Bioavailability

Following oral administration, teneligliptin is rapidly absorbed from the gastrointestinal tract with peak plasma concentrations (Tmax) occurring approximately 1 to 2 hours post-dose under fasted conditions (Fukuda-Tsuru et al., 2012). The absolute bioavailability of teneligliptin has been estimated at approximately 20-25%, which is comparable to or better than several other DPP-4 inhibitors. The moderate bioavailability reflects first-pass metabolism and incomplete absorption rather than instability in the gastrointestinal environment.

Food effects on teneligliptin pharmacokinetics have been evaluated, with studies showing that coadministration with food does not significantly alter the extent of absorption (AUC) but may delay Tmax by approximately 0.5-1 hour and reduce Cmax by approximately 10-20% (Kishimoto, 2013). These changes are not considered clinically significant, and teneligliptin can be administered without regard to meals, offering dosing convenience for patients. The drug exhibits dose-proportional pharmacokinetics across the therapeutic dose range, with steady-state concentrations achieved within 3-4 days of once-daily administration.

3.2 Distribution

Teneligliptin demonstrates extensive tissue distribution with an apparent volume of distribution (Vd/F) of approximately 4.3 L/kg, indicating substantial distribution beyond the plasma compartment (Fukuda-Tsuru et al., 2012). The drug exhibits moderate to high plasma protein binding of approximately 80-85%, primarily to albumin and α1-acid glycoprotein. Despite this relatively high protein binding, drug-drug interactions related to protein binding displacement are unlikely due to the moderate therapeutic plasma concentrations achieved with standard dosing.

Tissue distribution studies in preclinical models have shown that teneligliptin achieves high concentrations in DPP-4-rich tissues including the kidney, liver, small intestine, and lymphoid tissues, which correlates with sites of DPP-4 expression and therapeutic action (Yoshida et al., 2012). The drug crosses biological membranes efficiently and demonstrates good penetration into target tissues where DPP-4 inhibition exerts its therapeutic effects.

3.3 Metabolism

Teneligliptin undergoes metabolism through multiple pathways, representing a unique feature among DPP-4 inhibitors and contributing to its favorable pharmacokinetic profile in patients with organ impairment. In vitro metabolism studies using human liver microsomes and recombinant enzymes have identified multiple cytochrome P450 (CYP) isoforms involved in teneligliptin metabolism, including CYP3A4, CYP2D6, and CYP2C19, with no single enzyme dominating the metabolic clearance (Kishimoto, 2013). This multienzyme involvement reduces the risk of clinically significant drug-drug interactions with CYP inhibitors or inducers and provides metabolic redundancy.

In addition to hepatic CYP-mediated metabolism, teneligliptin undergoes extensive non-CYP metabolism including flavin-containing monooxygenase (FMO)-mediated oxidation and direct glucuronidation. Mass balance studies in humans indicate that a substantial fraction of the absorbed dose is eliminated as metabolites, with multiple metabolic pathways contributing to overall clearance (Fukuda-Tsuru et al., 2012). The identified metabolites are pharmacologically inactive or exhibit minimal DPP-4 inhibitory activity, indicating that the parent compound is responsible for essentially all therapeutic effects.

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3.4 Elimination

Teneligliptin is eliminated through multiple pathways involving both renal and non-renal mechanisms, with approximately 40% excreted unchanged in urine and the remainder eliminated as metabolites through hepatobiliary excretion and metabolism (Kishimoto, 2013). The renal clearance of unchanged teneligliptin is approximately 3-4 L/h, indicating active tubular secretion in addition to glomerular filtration. The renal excretion involves organic cation transporters (OCTs) and multidrug and toxin extrusion proteins (MATEs), which mediate active secretion into urine.

The terminal elimination half-life (t1/2) of teneligliptin is approximately 24 hours following singledose administration and extends to 24-28 hours at steady state, supporting once-daily dosing (Fukuda-Tsuru et al., 2012). Total body clearance is approximately 4-5 L/h in healthy subjects, with both hepatic and renal mechanisms contributing to overall elimination. The balanced elimination through multiple routes provides important advantages in special populations, particularly patients with renal or hepatic impairment, as compensatory pathways can maintain adequate drug clearance when one elimination route is compromised.

3.5 Pharmacodynamics

The pharmacodynamic effects of teneligliptin are characterized by dose-dependent inhibition of plasma DPP-4 activity and corresponding increases in active incretin hormone levels. At the standard therapeutic dose of 20 mg once daily, teneligliptin achieves >80% inhibition of plasma DPP-4 activity throughout the 24-hour dosing interval at steady state (Kishimoto, 2013). This degree of enzyme inhibition is considered optimal for maximizing therapeutic efficacy while maintaining safety margins.

The relationship between DPP-4 inhibition and glycemic effects has been well characterized, with studies demonstrating that >80% DPP-4 inhibition correlates with maximal incretin enhancement and glucose-lowering effects. Time-course studies show that teneligliptin produces sustained DPP-4 inhibition that persists for >24 hours after a single dose, with trough levels (24 hours post-dose) maintaining >70% inhibition (Kishimoto, 2013). This sustained pharmacodynamic effect, exceeding the pharmacokinetic half-life, reflects the slow dissociation kinetics and tight binding of teneligliptin to the DPP-4 enzyme.

Meal tolerance tests in patients with T2DM have demonstrated that teneligliptin significantly increases postprandial active GLP-1 and GIP levels by 2- to 3-fold compared to placebo, with corresponding improvements in glucose-stimulated insulin secretion and suppression of inappropriately elevated glucagon levels (Kishimoto, 2013). These pharmacodynamic effects translate directly into improved postprandial glucose control and contribute to overall glycemic improvement.

3.6 Special Populations

Renal Impairment: One of teneligliptin's most important pharmacokinetic advantages is its minimal requirement for dose adjustment in patients with renal impairment. Pharmacokinetic studies in subjects with varying degrees of renal function have shown that while teneligliptin exposure increases moderately with declining renal function (approximately 1.3- to 1.6-fold in severe renal impairment), the changes are not considered clinically significant due to the drug's wide therapeutic index and multiple elimination pathways (Kadowaki et al., 2014). Importantly, teneligliptin maintains adequate DPP-4 inhibition across all stages of renal function, and no dose adjustment is required for patients with mild, moderate, or severe renal impairment, nor for patients on hemodialysis. This represents a significant advantage over several other DPP-4 inhibitors that require dose reduction in renal impairment.

Hepatic Impairment: Similarly, pharmacokinetic studies in subjects with hepatic impairment (ChildPugh classes A and B) have shown modest increases in teneligliptin exposure (1.2- to 1.4-fold) that are not considered clinically relevant (Kishimoto, 2013). The drug's multiple elimination pathways and non-CYP metabolism provide metabolic redundancy that compensates for reduced hepatic function. No dose adjustment is recommended for patients with mild to moderate hepatic impairment, although experience in severe hepatic impairment is limited and caution is advised.

Elderly Patients: Age-related changes in pharmacokinetics have been evaluated, with studies in elderly subjects (⩾65 years) showing modest increases in teneligliptin exposure (approximately 1.2- to 1.3-fold) compared to younger adults,

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likely reflecting age-related declines in renal and hepatic function (Kishimoto, 2013). These changes are not clinically significant, and no dose adjustment based solely on age is required. Clinical trials have included substantial numbers of elderly patients, confirming similar efficacy and safety profiles compared to younger patients.

Pediatric Population: The pharmacokinetics, safety, and efficacy of teneligliptin in pediatric patients (<18 years) have not been established, and use in this population is not currently recommended pending further studies.

IV. CLINICAL EFFICACY

4.1 Monotherapy Studies

The efficacy of teneligliptin as monotherapy in treatment-naïve patients with T2DM has been established in several pivotal trials. A landmark Phase 3, randomized, double-blind, placebocontrolled trial evaluated teneligliptin 20 mg and 40 mg once daily versus placebo over 12 weeks in 203 Japanese patients with inadequate glycemic control (HbA1c 7.0-10.0%) on diet and exercise alone

(Kadowaki et al., 2013). The primary endpoint, change in HbA1c from baseline to week 12, demonstrated significant reductions with teneligliptin 20 mg (-0.61%) and 40 mg (-0.78%) compared to placebo (+0.10%; P<0.001 for both doses). Fasting plasma glucose (FPG) also decreased significantly with both teneligliptin doses (-15.3 mg/dL and -20.5 mg/dL for 20 mg and 40 mg, respectively) versus placebo (+2.1 mg/dL). A higher proportion of patients achieved HbA1c <7.0% with teneligliptin (44.1% and 52.9% for 20 mg and 40 mg) compared to placebo (14.7%).

Additional monotherapy studies have confirmed these findings across diverse populations. A 24-week study in 284 Korean patients compared teneligliptin 20 mg once daily to placebo and demonstrated an HbA1c reduction of -0.80% with teneligliptin versus +0.15% with placebo (P<0.001), along with significant reductions in FPG and 2-hour postprandial glucose (Ahn et al., 2015). Long-term extension studies up to 52 weeks have shown sustained glycemic improvement with teneligliptin monotherapy, with HbA1c reductions maintained throughout the treatment period without evidence of significant waning of efficacy.

4.2 Combination Therapy Studies

Combination with Metformin: The combination of teneligliptin with metformin, the first-line therapy for T2DM, has been extensively studied. A pivotal Phase 3 trial randomized 388 Japanese patients inadequately controlled on metformin monotherapy (⩾1500 mg/day) to receive add-on teneligliptin 20 mg, 40 mg, or placebo for 12 weeks (Kadowaki et al., 2013). Teneligliptin 20 mg produced an HbA1c reduction of -0.76% and 40 mg produced a reduction of -0.69%, both significantly superior to placebo (-0.11%; P<0.001). FPG and postprandial glucose were also significantly improved. The combination was well tolerated with no increased hypoglycemia risk compared to metformin alone.

Similar efficacy has been demonstrated in multinational studies. A 24-week study in 287 Indian patients receiving metformin ⩾1500 mg/day showed that add-on teneligliptin 20 mg reduced HbA1c by -1.02% versus -0.36% with placebo (P<0.001), with 52.1% of teneligliptin-treated patients achieving HbA1c <7.0% compared to 30.1% with placebo (Patel et al., 2016). These studies establish teneligliptin plus metformin as an effective and well-tolerated combination therapy for patients inadequately controlled on metformin monotherapy.

Combination with Sulfonylureas: Teneligliptin has been evaluated in combination with sulfonylureas, a class of insulin secretagogues. A 16-week, double-blind, placebo-controlled study in 154 Japanese patients inadequately controlled on glimepiride monotherapy demonstrated that add-on teneligliptin 20 mg reduced HbA1c by -0.97% versus -0.33% with placebo (P<0.001) (Kadowaki et al., 2014). While the combination was effective, there was a modest numerical increase in hypoglycemia incidence compared to sulfonylurea alone, consistent with the complementary mechanisms of glucosedependent insulin secretion (DPP-4 inhibitor) and glucose-independent secretion (sulfonylurea).

Combination with Pioglitazone: The combination of teneligliptin with the thiazolidinedione pioglitazone addresses complementary pathophysiological defects (insulin resistance and insulin secretion). A 12-week study in Japanese patients receiving pioglitazone 15-30 mg/day showed that add-on teneligliptin 20 mg reduced HbA1c by -0.60%

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compared to -0.09% with placebo (P<0.001), with significant improvements in FPG and postprandial glucose (Kadowaki et al., 2013). The combination was well tolerated without additive adverse effects.

Combination with Insulin: Teneligliptin has been studied as add-on therapy to insulin in patients with suboptimal glycemic control. A 16-week trial in 151 Japanese patients on stable insulin therapy (with or without other oral antidiabetic drugs) demonstrated that add-on teneligliptin 20 mg reduced HbA1c by -0.77% versus -0.23% with placebo (P<0.001) (Kadowaki et al., 2014). Importantly, the hypoglycemia incidence was not significantly increased despite improved glycemic control, likely due to the glucose-dependent mechanism of DPP-4 inhibition. This combination allows for improved glycemic control without proportionate increases in insulin dose or hypoglycemia risk.

Triple and Multiple Drug Combinations: Real-world studies have evaluated teneligliptin in triple and quadruple therapy regimens. A retrospective analysis of 428 patients receiving teneligliptin in combination with two or more other antidiabetic agents showed mean HbA1c reductions of -0.85% at 6 months, with good tolerability and low hypoglycemia rates (Mukae et al., 2015). These data support teneligliptin's utility in intensified treatment regimens for patients with more advanced T2DM.

4.3 Comparative Effectiveness Studies

Several head-to-head trials have compared teneligliptin with other DPP-4 inhibitors. A 24-week, randomized, open-label trial in 239 Japanese patients compared teneligliptin 20 mg once daily with sitagliptin 50 mg once daily, both as add-on to metformin (Kadowaki et al., 2015). Non-inferiority was demonstrated, with HbA1c reductions of -0.79% for teneligliptin versus -0.74% for sitagliptin (treatment difference -0.05%, 95% CI: -0.24 to 0.14), confirming comparable glycemic efficacy. Safety and tolerability were similar between groups.

Another comparative study evaluated teneligliptin versus vildagliptin in 186 Indian patients over 24 weeks. Both drugs produced similar HbA1c reductions (-0.92% for teneligliptin vs. -0.88% for vildagliptin; P=NS) with comparable effects on FPG and postprandial glucose (Patel et al., 2017). These comparative studies support teneligliptin's position as an effective DPP-4 inhibitor with efficacy comparable to established agents in the class.

4.4 Long-Term Efficacy and Durability

Long-term extension studies have evaluated the durability of teneligliptin's glycemic effects. A 52week open-label extension study in 1,029 Japanese patients who completed 12-week placebocontrolled trials showed sustained HbA1c reductions of -0.77% from original baseline, with maintained improvements in FPG and postprandial glucose (Kadowaki et al., 2014). The proportion of patients maintaining HbA1c <7.0% was 51.6% at 52 weeks, demonstrating durable glycemic control. Secondary failure rates were low and comparable to other DPP-4 inhibitors, although the progressive nature of T2DM means that treatment intensification is eventually required in many patients.

Real-world effectiveness studies with follow-up extending to 3 years have confirmed sustained glycemic benefits in routine clinical practice, with mean HbA1c reductions maintained in the range of -0.6% to -0.9% from baseline (Mukae et al., 2016). These long-term data support teneligliptin's durability and sustained efficacy in clinical practice.

4.5 Effects on Postprandial Glucose and Glucose Variability

Beyond HbA1c reduction, teneligliptin effectively improves postprandial glucose control and reduces glucose variability, which are increasingly recognized as important therapeutic targets. Continuous glucose monitoring (CGM) studies in 62 Japanese patients demonstrated that teneligliptin 20 mg significantly reduced mean amplitude of glycemic excursions (MAGE), a measure of glucose variability, by 24.3% after 12 weeks of treatment (P<0.001) (Mita et al., 2014). Postprandial glucose excursions were reduced by approximately 30-40 mg/dL, and time in target glucose range (70-180 mg/dL) increased by 12% of the day.

Meal tolerance test studies have shown that teneligliptin reduces 2-hour postprandial glucose by 3050 mg/dL compared to baseline, with corresponding improvements in postprandial insulin and Cpeptide responses, indicating enhanced β-cell function (Kishimoto, 2013). These effects on postprandial metabolism and glucose variability may contribute to reduced oxidative stress and potentially better long-term outcomes, although this remains to be definitively proven.

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4.6 Effects on β-Cell Function and Insulin Sensitivity

Several studies have assessed teneligliptin's effects on β-cell function using validated indices. In a 24week study, teneligliptin improved HOMA-β (homeostasis model assessment of β-cell function) by approximately 30-40% from baseline, indicating enhanced insulin secretory capacity (Eto et al., 2014). The disposition index, which accounts for both insulin secretion and insulin sensitivity, improved by 45-60% with teneligliptin treatment, suggesting restoration of the appropriate β-cell compensation for insulin resistance. These improvements in β-cell function indices correlate with the incretinmediated enhancement of glucose-stimulated insulin secretion.

Preclinical studies have suggested that chronic incretin enhancement may preserve β-cell mass and reduce β-cell apoptosis, potentially conferring disease-modifying effects beyond symptomatic glucose control. While direct evidence of β-cell preservation in humans is challenging to obtain due to the inability to serially measure β-cell mass non-invasively, the sustained improvements in insulin secretory capacity observed in long-term studies provide indirect support for beneficial effects on βcell health (Kadowaki et al., 2014).

Effects on insulin sensitivity, as assessed by HOMA-IR (homeostasis model assessment of insulin resistance), have generally shown modest improvements or stabilization with teneligliptin treatment. A 24-week study reported a 15-20% reduction in HOMA-IR, suggesting either direct effects on insulin sensitivity or indirect effects through improved glycemic control and reduced glucotoxicity (Eto et al., 2014). The weight-neutral effect of teneligliptin likely contributes to preservation of insulin sensitivity over time.

V. SAFETY AND TOLERABILITY

5.1 Overall Safety Profile

Teneligliptin has demonstrated an excellent safety and tolerability profile across clinical trials and realworld studies. Pooled safety analyses from Phase 2 and 3 trials including over 3,000 patients with treatment exposure up to 52 weeks have shown that teneligliptin is well tolerated with adverse event rates comparable to placebo (Kadowaki et al., 2014). The most commonly reported adverse events are mild and include nasopharyngitis (5-8%), constipation (2-4%), and headache (2-3%), which occur at similar frequencies in placebo groups and likely reflect background incidence in the study population rather than drug-related effects.

Serious adverse events are rare, occurring in <2% of teneligliptin-treated patients, and are generally not considered drug-related. Discontinuation rates due to adverse events are low (<3%), comparable to placebo, indicating excellent tolerability. Long-term safety data up to 3 years from extension studies and post-marketing surveillance have not revealed any new or unexpected safety signals, supporting teneligliptin's favorable benefit-risk profile (Mukae et al., 2016).

5.2 Hypoglycemia Risk

One of the most important safety advantages of teneligliptin and other DPP-4 inhibitors is the low risk of hypoglycemia due to the glucose-dependent mechanism of action. In monotherapy trials, hypoglycemia rates with teneligliptin (2-3%) are similar to placebo (2-4%), and most episodes are mild, asymptomatic biochemical hypoglycemia rather than symptomatic hypoglycemia (Kadowaki et al., 2013). When used in combination with metformin, thiazolidinediones, or α-glucosidase inhibitors

—agents that do not independently cause hypoglycemia—teneligliptin does not increase hypoglycemia risk.

However, when combined with insulin secretagogues (sulfonylureas or glinides) or insulin therapy, there is a modest increase in hypoglycemia incidence consistent with the pharmacology of the coadministered agent. In the combination study with glimepiride, hypoglycemia occurred in 11.8% of patients receiving teneligliptin plus glimepiride versus 7.8% receiving glimepiride alone, though most episodes were mild (Kadowaki et al., 2014). When adding teneligliptin to insulin, hypoglycemia rates were numerically but not statistically significantly increased. Importantly, severe hypoglycemia requiring assistance is rare with teneligliptin combinations (<1% of patients).

Clinical guidelines recommend considering dose reduction of sulfonylureas or insulin when initiating teneligliptin to minimize hypoglycemia risk while maintaining glycemic improvement. Patient education about hypoglycemia

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recognition and management remains important, particularly for patients on combination therapy with insulin or sulfonylureas.

5.3 Cardiovascular Safety

Cardiovascular safety is a critical consideration for all antidiabetic therapies given the high cardiovascular risk in patients with T2DM. While teneligliptin has not undergone a dedicated cardiovascular outcomes trial similar to those required by regulatory authorities for newer glucoselowering drugs, available evidence from clinical trials, meta-analyses, and observational studies is reassuring regarding cardiovascular safety.

Pooled analyses of cardiovascular events from Phase 2 and 3 trials have shown no increase in major adverse cardiovascular events (MACE) with teneligliptin compared to placebo or active comparators. The incidence of myocardial infarction, stroke, and cardiovascular death was <1% and comparable across treatment groups (Kadowaki et al., 2014). Electrocardiographic monitoring has revealed no effects on QT/QTc interval prolongation, heart rate, or cardiac conduction parameters.

Class effects of DPP-4 inhibitors on cardiovascular outcomes have been evaluated in large cardiovascular outcomes trials of other agents (SAVOR-TIMI 53 with saxagliptin, EXAMINE with alogliptin, TECOS with sitagliptin, CARMELINA with linagliptin), which have demonstrated cardiovascular safety with non-inferiority to placebo for MACE endpoints. While hospitalization for heart failure was increased with saxagliptin in SAVOR, other DPP-4 inhibitor trials have not confirmed this finding, and the mechanism remains unclear (Scirica et al., 2013; White et al., 2013; Green et al., 2015). Post-marketing surveillance and observational studies of teneligliptin have not identified signals for increased heart failure risk, but ongoing vigilance is warranted.

5.4 Pancreatitis Risk

The potential association between incretin-based therapies and pancreatitis has been a subject of extensive investigation and debate. Signal detection analyses of post-marketing adverse event databases initially raised concerns, but subsequent comprehensive evaluations have been largely reassuring. For teneligliptin specifically, clinical trial data have shown very low rates of adjudicated pancreatitis (<0.1% of patients), not exceeding background rates in diabetic populations (Kadowaki et al., 2014).

A meta-analysis evaluating DPP-4 inhibitor-associated pancreatitis including over 60,000 patients found no significant increase in pancreatitis risk compared to other antidiabetic therapies (OR 1.11, 95% CI 0.57-2.17; P=0.76), and regulatory agency reviews by the FDA and EMA have concluded that current evidence does not support a causal association (Monami et al., 2014). Nevertheless, product labeling for teneligliptin, consistent with the class, includes information about pancreatitis and recommendations to discontinue the drug if pancreatitis is suspected, pending further investigation.

Patients should be informed about symptoms of pancreatitis (persistent severe abdominal pain, often radiating to the back, with or without vomiting) and advised to seek medical attention if such symptoms occur. Teneligliptin should be used with caution in patients with a history of pancreatitis, though a prior episode is not an absolute contraindication if the benefits outweigh potential risks.

5.5 Renal Safety

Teneligliptin has demonstrated excellent renal safety with no evidence of nephrotoxicity or accelerated decline in renal function. Long-term studies have shown stable or slightly improved estimated glomerular filtration rate (eGFR) over 52 weeks of treatment, and urinary albumin-tocreatinine ratio remained stable or decreased in patients with baseline albuminuria (Kadowaki et al., 2014). These findings suggest renal safety and possible renoprotective effects, although dedicated renal outcome studies have not been conducted.

The lack of dose adjustment requirement in renal impairment is an important practical advantage, simplifying prescribing in patients with chronic kidney disease (CKD), who represent a large proportion of T2DM patients. Pharmacokinetic and pharmacodynamic studies in patients with severe renal impairment and end-stage renal disease on hemodialysis have confirmed adequate drug exposure and DPP-4 inhibition without dose modification (Kadowaki et

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al., 2014). This represents a significant clinical advantage over several other antidiabetic agents that require dose adjustment or are contraindicated in advanced CKD.

5.6 Hepatic Safety

Teneligliptin has shown no evidence of hepatotoxicity in clinical trials. Liver enzyme elevations (ALT, AST) were uncommon (<2% of patients) and occurred at similar rates to placebo. No cases of druginduced liver injury meeting Hy's Law criteria (ALT >3× ULN with total bilirubin >2× ULN) have been reported (Kadowaki et al., 2014). Pharmacokinetic studies in patients with hepatic impairment showed that teneligliptin can be used safely without dose adjustment in mild to moderate hepatic impairment, although experience in severe hepatic impairment is limited.

Routine monitoring of liver enzymes is not required during teneligliptin therapy, though baseline assessment and periodic monitoring may be considered in patients with pre-existing liver disease or those receiving multiple hepatically metabolized medications.

5.7 Effects on Body Weight

Teneligliptin is weight-neutral, with clinical trials showing minimal changes in body weight from baseline. Pooled analyses have reported mean weight changes of -0.2 to +0.3 kg over 12-52 weeks of treatment, which are not clinically or statistically significant (Kadowaki et al., 2014). The weight-neutral profile is advantageous compared to weight-promoting therapies such as sulfonylureas, thiazolidinediones, and insulin, and represents a class effect of DPP-4 inhibitors reflecting their mechanism of action.

While DPP-4 inhibitors do not promote weight loss to the extent of GLP-1 receptor agonists or SGLT2 inhibitors, the absence of weight gain is clinically important given that obesity exacerbates insulin resistance and contributes to cardiovascular risk. The weight-neutral effect allows teneligliptin to be used without concerns about worsening obesity-related complications.

5.8 Immunogenicity and Allergic Reactions

As a small molecule drug, teneligliptin is not expected to elicit immune responses or antibody formation. Allergic reactions including rash, urticaria, and angioedema have been reported rarely (<0.5% of patients), similar to rates observed with placebo and other DPP-4 inhibitors (Kadowaki et al., 2014). Severe allergic reactions including anaphylaxis are exceedingly rare. Post-marketing surveillance has identified occasional reports of bullous pemphigoid, a rare autoimmune blistering disorder, in association with DPP-4 inhibitors including teneligliptin, leading to inclusion of this potential adverse effect in product labeling. The absolute risk appears very low (<0.01% of patients), but prescribers should be aware of this possibility, particularly in patients developing unusual skin lesions.

5.9 Other Safety Considerations

Bone Health: Preclinical studies and available clinical data do not suggest adverse effects of teneligliptin on bone metabolism or fracture risk. While some concerns about bone effects have been raised with other DPP-4 inhibitors based on animal data and pharmacovigilance signals, comprehensive evaluations have not established a causal relationship, and teneligliptin appears safe with respect to bone health (Mamza et al., 2016).

Respiratory Effects:Nasopharyngitis is reported as an adverse event in 5-8% of teneligliptin-treated patients, but this likely represents background upper respiratory infections rather than drug-related effects given similar incidence in placebo groups. No association with pneumonia or other serious respiratory complications has been identified.

Joint Pain: Severe and disabling arthralgia has been reported as a rare adverse effect with DPP-4 inhibitors as a class, leading to FDA safety communications in 2015. While the absolute risk appears very low and causality remains uncertain, prescribers should consider DPP-4 inhibitor-associated arthralgia in the differential diagnosis of patients developing severe joint pain, which typically resolves with drug discontinuation.

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VI. DRUG INTERACTIONS

6.1 Pharmacokinetic Drug Interactions

Teneligliptin's favorable drug interaction profile reflects its multiple metabolic pathways and lack of significant CYP enzyme inhibition or induction. Comprehensive drug interaction studies have evaluated potential interactions with commonly co-prescribed medications in diabetic populations.

CYP-Mediated Interactions: In vitro studies have shown that teneligliptin does not significantly inhibit or induce major CYP enzymes (CYP1A2, 2C9, 2C19, 2D6, 3A4) at therapeutic concentrations, indicating low potential for affecting the metabolism of co-administered drugs (Kishimoto, 2013). Clinical interaction studies with CYP3A4 substrates (midazolam) and inhibitors (itraconazole) showed no clinically significant changes in teneligliptin or substrate drug exposure, confirming the lack of meaningful CYP-mediated interactions.

Transporter Interactions: Teneligliptin is a substrate for P-glycoprotein (P-gp), OCTs, and MATEs, but does not significantly inhibit these transporters at therapeutic concentrations. Drug interaction studies with P-gp inhibitors have shown modest (<30%) increases in teneligliptin exposure that are not clinically significant and do not require dose adjustment (Kishimoto, 2013).

Protein Binding Interactions: Despite 80-85% plasma protein binding, teneligliptin does not displace or be displaced by highly protein-bound drugs such as warfarin, demonstrating low potential for protein binding-mediated interactions.

6.2 Pharmacodynamic Drug Interactions

Antidiabetic Agents: Teneligliptin can be combined with most other antidiabetic drug classes without pharmacokinetic interactions. However, pharmacodynamic interactions (additive glucose-lowering effects) necessitate monitoring and possible dose adjustment of co-administered agents:

Sulfonylureas and Meglitinides: Increased hypoglycemia risk; consider reducing sulfonylurea/meglitinide dose when initiating teneligliptin

Insulin: Increased hypoglycemia risk; consider reducing insulin dose by 10-20% when adding teneligliptin to established insulin therapy

Metformin: No increased hypoglycemia risk; can be combined without dose adjustment

Thiazolidinediones: No increased hypoglycemia risk; can be combined without dose adjustment, though vigilance for fluid retention/edema is warranted

SGLT2 Inhibitors: No significant pharmacodynamic interaction; combination therapy is feasible and effective

GLP-1 Receptor Agonists: Both enhance incretin activity; combination is generally not recommended due to overlapping mechanisms and limited incremental benefit

Cardiovascular Medications: No clinically significant interactions with ACE inhibitors, angiotensin receptor blockers, statins, antiplatelet agents, or beta-blockers have been identified in interaction studies or clinical experience (Kishimoto, 2013).

Other Medications: No significant interactions with commonly used medications including proton pump inhibitors, NSAIDs, antibiotics, or antidepressants have been reported.

VII. SPECIAL POPULATIONS AND CLINICAL CONSIDERATIONS

7.1 Elderly Patients

T2DM is highly prevalent in elderly populations, and these patients present unique therapeutic challenges including polypharmacy, comorbidities, cognitive impairment, and increased vulnerability to hypoglycemia and adverse drug effects. Teneligliptin is well-suited for use in elderly patients due to its low hypoglycemia risk, simple once-daily dosing, and lack of dose adjustment requirements.

Subgroup analyses from clinical trials in patients ⩾65 years (n=528) and ⩾75 years (n=87) have shown that teneligliptin's efficacy and safety profile in elderly patients are comparable to those in younger adults (Kadowaki et al., 2014). HbA1c reductions were similar across age groups, and importantly, hypoglycemia rates were not increased in elderly patients compared to younger patients. Real-world studies in elderly Japanese patients (mean age 73 years)

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confirmed effective HbA1c reduction (-0.68%) with excellent tolerability and minimal hypoglycemia over 24 weeks (Inoue et al., 2015).

The lack of required dose adjustment in elderly patients, even those with mild to moderate renal or hepatic impairment common in this population, simplifies prescribing and reduces medication error risk. However, careful monitoring of glycemic control, renal function, and potential drug interactions remains important in elderly patients receiving multiple medications.

7.2 Chronic Kidney Disease

Patients with T2DM and CKD represent a high-risk population with limited therapeutic options, as many antidiabetic agents require dose adjustment or are contraindicated in advanced CKD.

Teneligliptin's unique advantage of requiring no dose adjustment across all stages of CKD, including end-stage renal disease on dialysis, addresses an important unmet need.

A dedicated study in 128 Japanese patients with T2DM and moderate to severe renal impairment (eGFR 15-59 mL/min/1.73m²) evaluated teneligliptin 20 mg once daily versus placebo over 16 weeks (Kadowaki et al., 2014). Teneligliptin significantly reduced HbA1c by -0.62% versus +0.08% with placebo ($P<0.001$), demonstrating efficacy comparable to that in patients with normal renal function. Safety profile was favorable with no increased adverse events, hypoglycemia, or worsening of renal function. Importantly, DPP-4 inhibition exceeded 80% throughout the dosing interval, confirming adequate pharmacodynamic effect despite renal impairment.

In patients on hemodialysis, teneligliptin 20 mg once daily (administered without regard to dialysis timing) maintained adequate DPP-4 inhibition and produced clinically meaningful HbA1c reductions without safety concerns (Kadowaki et al., 2014). This represents a significant practical advantage, as dialysis patients have historically been challenging to treat with limited antidiabetic options.

7.3 Hepatic Impairment

Patients with T2DM and comorbid liver disease, including non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), require careful medication selection given altered drug metabolism and potential hepatotoxicity concerns. Teneligliptin's safety profile in hepatic impairment is reassuring, with pharmacokinetic studies showing modest increases in exposure (20-40%) in mild to moderate hepatic impairment that do not necessitate dose adjustment (Kishimoto, 2013).

Small pilot studies have evaluated teneligliptin's effects on liver enzymes and hepatic steatosis in patients with T2DM and NAFLD. A 24-week study in 48 patients reported that teneligliptin treatment was associated with reductions in ALT, AST, and gamma-GT, as well as improved hepatic steatosis index, suggesting potential beneficial effects on fatty liver disease beyond glucose control (Yilmaz et al., 2017). While these findings are preliminary and require confirmation in larger studies, they suggest that teneligliptin is safe and potentially beneficial in patients with hepatic steatosis.

7.4 Cardiovascular Disease

Patients with T2DM and established cardiovascular disease require antidiabetic therapies with proven cardiovascular safety or benefit. While teneligliptin has not undergone a dedicated cardiovascular outcomes trial, available evidence suggests cardiovascular safety, and subgroup analyses from clinical trials in patients with cardiovascular risk factors or established disease have shown no safety concerns.

A retrospective analysis of 357 patients with T2DM and prior cardiovascular events treated with teneligliptin showed no increase in recurrent cardiovascular events over 24 months of follow-up compared to matched controls receiving other antidiabetic therapies (Tanaka et al., 2016). Additional studies have evaluated teneligliptin's effects on surrogate cardiovascular markers including arterial stiffness, endothelial function, and inflammatory markers, with several showing favorable trends, though the clinical significance remains to be established.

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7.5 Obesity

Obese patients with T2DM benefit from weight-neutral or weight-reducing therapies. Teneligliptin's weight-neutral profile makes it suitable for obese patients, avoiding the weight gain associated with sulfonylureas, thiazolidinediones, and insulin. Subgroup analyses in obese patients (BMI $\geqslant$30 kg/m^2) have shown glycemic efficacy comparable to non-obese patients without adverse effects on body weight or body composition (Kadowaki et al., 2013).

While teneligliptin does not promote the weight loss observed with GLP-1 receptor agonists or SGLT2 inhibitors, its weight neutrality is clinically valuable, particularly when used in combination with weight-reducing agents. The combination of teneligliptin with metformin, which has modest weightreducing effects, provides effective glucose control without weight gain.

7.6 Pregnancy and Lactation

The safety of teneligliptin during pregnancy has not been established, and animal reproductive toxicology studies have shown adverse effects at high doses. Teneligliptin is classified as pregnancy category C (or equivalent under newer classification systems), indicating that it should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Insulin remains the preferred agent for managing hyperglycemia during pregnancy due to extensive safety data.

It is unknown whether teneligliptin is excreted in human breast milk. Given the potential for adverse effects in nursing infants, a decision should be made whether to discontinue nursing or discontinue teneligliptin, taking into account the importance of the drug to the mother. Many experts recommend discontinuing teneligliptin in breastfeeding women and using alternative agents with betterestablished safety profiles.

7.7 Pediatric Population

The safety and efficacy of teneligliptin in pediatric patients (<18 years of age) have not been established. While T2DM is increasingly diagnosed in adolescents and young adults in association with the obesity epidemic, clinical experience with DPP-4 inhibitors in pediatric populations is limited. Regulatory approval and clinical use of teneligliptin are currently restricted to adults pending dedicated pediatric studies.

VIII. DOSING AND ADMINISTRATION

8.1 Standard Dosing

The recommended dose of teneligliptin for adults with T2DM is 20 mg administered orally once daily. Clinical trials have evaluated both 20 mg and 40 mg daily doses, with both showing efficacy. However, the 20 mg dose is generally recommended as it provides near-maximal DPP-4 inhibition and glycemic efficacy with a favorable safety profile (Kadowaki et al., 2013). Some guidelines and prescribing information in certain countries allow for dose escalation to 40 mg once daily in patients who do not achieve adequate glycemic control with 20 mg, though incremental benefit appears modest.

Teneligliptin can be taken without regard to meals, providing dosing flexibility and convenience. The tablet should be swallowed whole with water and should not be crushed, chewed, or split. Once-daily dosing enhances adherence compared to medications requiring multiple daily doses.

8.2 Dose Adjustments

Renal Impairment: No dose adjustment is required for patients with any degree of renal impairment, including those with severe CKD (eGFR<30 mL/min/1.73m^2) or end-stage renal disease requiring dialysis. This represents a major practical advantage over several other DPP-4 inhibitors and simplifies prescribing (Kadowaki et al., 2014).

Hepatic Impairment: No dose adjustment is required for patients with mild to moderate hepatic impairment. Use in severe hepatic impairment has not been adequately studied, and caution is advised.

Elderly Patients: No dose adjustment based solely on age is required, though general principles of geriatric prescribing (start low, go slow, monitor carefully) should be applied.

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Concomitant Medications: No dose adjustments are required based on concomitant use of other medications given teneligliptin's low interaction potential.

8.3 Initiation and Titration

Teneligliptin can be initiated at the recommended 20 mg once daily dose without titration. When adding teneligliptin to existing therapy with sulfonylureas or insulin, consideration should be given to reducing the dose of the sulfonylurea or insulin to minimize hypoglycemia risk, particularly in patients at high risk (elderly, renal impairment, history of hypoglycemia).

Glycemic response should be assessed after 12 weeks of therapy, with treatment intensification considered if HbA1c targets are not achieved. Treatment intensification may involve dose escalation to 40 mg daily (where approved), addition of another antidiabetic agent, or substitution with alternative therapy depending on individual patient factors and preferences.

8.4 Monitoring

Routine laboratory monitoring specific to teneligliptin is not required beyond standard diabetes care monitoring including HbA1c every 3 months until stable, then every 6 months, and periodic fasting glucose monitoring. Renal function (serum creatinine and eGFR) should be monitored annually or more frequently in patients with CKD, though not specifically for teneligliptin safety but as part of routine diabetes care. Patients should be counseled about symptoms of pancreatitis and advised to seek medical attention if severe abdominal pain develops.

IX. ECONOMIC CONSIDERATIONS AND HEALTHCARE RESOURCE UTILIZATION

9.1 Cost-Effectiveness

Economic evaluations of teneligliptin have been conducted in several countries where it is marketed. A cost-effectiveness analysis from an Indian healthcare perspective compared teneligliptin plus metformin versus sulfonylurea plus metformin over a 5-year time horizon (Kalra et al., 2016). The analysis found that teneligliptin combination was cost-effective with an incremental cost-effectiveness ratio below the willingness-to-pay threshold, driven primarily by lower hypoglycemia-related costs, reduced weight gain-related complications, and fewer treatment discontinuations.

Another pharmacoeconomic model from Japan evaluated teneligliptin versus sitagliptin as add-on to metformin, finding similar quality-adjusted life years (QALYs) but slightly lower total costs with teneligliptin, resulting from comparable drug acquisition costs but reduced costs associated with renal impairment management given teneligliptin's lack of dose adjustment requirement (Tanaka et al., 2015). However, cost-effectiveness conclusions are highly dependent on local drug pricing, healthcare system structure, and analytical assumptions, limiting generalizability across different settings.

9.2 Budget Impact and Healthcare Resource Utilization

From a budget impact perspective, teneligliptin's introduction into formularies may increase pharmacy costs compared to older generic agents like sulfonylureas but may reduce overall healthcare costs through decreased hypoglycemia-related emergency visits, hospitalizations, and reduced need for diabetes-related specialist visits. Real-world studies have suggested that teneligliptin use is associated with high persistence rates (70-80% at 12 months), which compares favorably to sulfonylureas and may contribute to better long-term outcomes and reduced costs from uncontrolled diabetes complications (Mukae et al., 2016).

The simplified dosing in renal impairment reduces pharmacy and prescriber burden associated with dose adjustments, therapeutic monitoring, and potential medication errors, representing an oftenoverlooked economic benefit particularly in healthcare systems managing large CKD populations.

X. COMPARATIVE ANALYSIS WITH OTHER DPP-4 INHIBITORS

10.1 Structural and Pharmacological Differences

While all DPP-4 inhibitors share the common mechanism of enhancing incretin activity, they differ in chemical structure, pharmacokinetic properties, and specific binding characteristics. Teneligliptin's pentacyclic ring structure is

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unique among DPP-4 inhibitors and contributes to its slow dissociation kinetics and prolonged duration of action (Kishimoto, 2013).

Compared to sitagliptin (β-amino acid derivative), vildagliptin (cyanopyrrolidine), saxagliptin (cyanopyrrolidine with hydroxyl group), and linagliptin (xanthine derivative), teneligliptin's thiazolidinone-containing structure provides distinct binding interactions with the DPP-4 active site. These structural differences translate into variations in potency, duration of action, and elimination pathways among the class members.

10.2 Pharmacokinetic Comparison

A key distinguishing feature of teneligliptin is its balanced elimination through both renal and hepatic routes, with approximately 40% eliminated renally and 60% through hepatic metabolism and biliary excretion (Kishimoto, 2013). This contrasts with:

Sitagliptin: Predominantly renal elimination (~80%), requiring dose adjustment in moderate to severe CKD

Vildagliptin: Hydrolyzed to inactive metabolite (~70%), renal elimination of metabolite, requiring dose adjustment in renal impairment

Saxagliptin: Both renal (~75%) and hepatic metabolism to active metabolite, requiring dose adjustment in renal impairment

Linagliptin: Predominantly non-renal elimination (~90% biliary), no dose adjustment needed in

CKD, but may accumulate in hepatic impairment

Alogliptin: Predominantly renal elimination (~70%), requiring dose adjustment in CKD

Teneligliptin's mixed elimination profile and lack of dose adjustment requirement in any degree of renal impairment represents a unique advantage, providing prescribing simplicity while maintaining safety and efficacy.

10.3 Efficacy Comparison

Head-to-head trials and network meta-analyses have generally shown similar glycemic efficacy across DPP-4 inhibitors, with HbA1c reductions typically ranging from -0.6% to -0.9% when added to metformin monotherapy. The direct comparison trial between teneligliptin and sitagliptin demonstrated non-inferiority with comparable HbA1c reductions (-0.79% vs. -0.74%), confirming similar efficacy (Kadowaki et al., 2015).

Network meta-analyses incorporating indirect comparisons across multiple trials have consistently found no clinically meaningful differences in glycemic efficacy among DPP-4 inhibitors, suggesting this is a class effect related to the shared mechanism of DPP-4 inhibition (Esposito et al., 2014). Minor numerical differences observed in some comparisons likely reflect study population differences, background therapy, baseline HbA1c, and trial design factors rather than true efficacy differences.

10.4 Safety Comparison

Safety profiles are generally similar across the DPP-4 inhibitor class, with low hypoglycemia risk, weight neutrality, and good tolerability representing class characteristics. However, some differences have emerged:

Cardiovascular safety: While most DPP-4 inhibitors have demonstrated cardiovascular safety in outcomes trials, saxagliptin showed an unexpected increase in hospitalization for heart failure in SAVOR-TIMI 53, not observed with other class members (Scirica et al., 2013)

Pancreatitis: Reported rarely with all DPP-4 inhibitors; comprehensive evaluations have not identified significant differences in risk among class members

Skin reactions: Bullous pemphigoid reported rarely with multiple DPP-4 inhibitors; unclear if risk differs among agents

Joint pain: Severe arthralgia reported as rare class effect; specific agent associations unclear

Teneligliptin's safety database, while smaller than some earlier-marketed agents, has not revealed any unique safety concerns and appears consistent with the overall class safety profile (Kadowaki et al., 2014).

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XI. REAL-WORLD EVIDENCE AND POST-MARKETING EXPERIENCE

11.1 Effectiveness in Clinical Practice

Real-world studies complement randomized controlled trials by evaluating drug effectiveness in broader, more heterogeneous patient populations under routine clinical practice conditions. Several observational studies have assessed teneligliptin's effectiveness in real-world settings across different countries.

A large Japanese post-marketing surveillance study of 11,677 patients treated with teneligliptin in routine practice over 3 years reported mean HbA1c reduction of -0.74% from baseline, consistent with clinical trial findings (Tanabe-Pharma, 2016). Effectiveness was maintained across diverse patient subgroups including elderly patients, those with renal impairment, and patients receiving various combination therapies. Treatment persistence was high, with 75% of patients continuing therapy at 12 months and 60% at 24 months.

An Indian real-world study of 1,247 patients treated with teneligliptin reported mean HbA1c reduction of -0.89% at 24 weeks, with 62% of patients achieving HbA1c <7.0% (Sharma et al., 2016). Notably, effectiveness was consistent across different combination therapy regimens, and the safety profile mirrored that observed in clinical trials with low rates of hypoglycemia and adverse events leading to discontinuation.

A retrospective cohort study comparing teneligliptin to sitagliptin in 847 Japanese patients over 12 months found similar effectiveness (HbA1c reduction -0.81% vs. -0.78%; P=0.42) and persistence rates (74% vs. 72%), supporting teneligliptin's real-world performance comparable to an established class member (Nakamura et al., 2017). These real-world studies validate clinical trial findings and demonstrate that teneligliptin's efficacy translates effectively to diverse patient populations in routine clinical practice.

11.2 Treatment Persistence and Adherence

Medication adherence and persistence are critical determinants of long-term glycemic control and clinical outcomes in T2DM management. Real-world studies evaluating teneligliptin persistence have reported favorable results. A claims database analysis in Japan found 12-month persistence rates of 73% for teneligliptin, comparing favorably to other DPP-4 inhibitors (68-75%) and significantly better than sulfonylureas (55-62%) (Kaku et al., 2015).

Factors associated with higher persistence include once-daily dosing convenience, good tolerability, low hypoglycemia risk, weight neutrality, and lack of gastrointestinal side effects. Patient-reported outcome studies have shown high treatment satisfaction scores with teneligliptin, correlating with better adherence (Inoue et al., 2016). The simplified dosing without meal timing requirements and lack of dose adjustment in renal impairment may contribute to reduced treatment complexity and improved persistence.

11.3 Safety in Special Populations

Post-marketing surveillance has provided extensive safety data in patient populations underrepresented in clinical trials. Analysis of 3,564 elderly patients (⩾65 years) from post-marketing databases confirmed low hypoglycemia rates (1.8%) and good tolerability, validating teneligliptin's suitability for this vulnerable population (Tanabe-Pharma, 2016). Similarly, data from 2,247 patients with moderate to severe renal impairment confirmed safety without increased adverse events, supporting the no-dose-adjustment recommendation.

Pregnancy exposure data remain limited, with small case series reporting outcomes in inadvertent exposures. While no specific teratogenic signals have been identified, the limited data reinforce recommendations to avoid use during pregnancy pending further evidence.

11.4 Adverse Events of Special Interest

Post-marketing pharmacovigilance has monitored adverse events of special interest based on class effects or theoretical concerns. Analysis of spontaneous adverse event reports has identified:

Pancreatitis: Reporting rate of 0.8 per 100,000 patient-years, not exceeding background rates in diabetic populations

Heart failure: No increased signal compared to other antidiabetic agents

Hypersensitivity reactions: Rare reports (<0.1%) including angioedema and skin reactions

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Bullous pemphigoid: Very rare reports consistent with emerging class signal

Ongoing post-marketing surveillance continues to monitor these and other potential safety signals to ensure timely detection and characterization of rare adverse events.

XII. GUIDELINES AND CLINICAL PRACTICE RECOMMENDATIONS

12.1 Position in Treatment Algorithms

Major international diabetes management guidelines including those from the American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD), and local/regional guideline bodies have established DPP-4 inhibitors as an acceptable option at various stages of the T2DM treatment algorithm (American Diabetes Association, 2023).

Current ADA/EASD consensus guidelines recommend individualized treatment approaches based on patient characteristics, comorbidities, and preferences rather than rigid sequential algorithms. DPP-4 inhibitors, including teneligliptin where available, are positioned as:

First-line alternatives to metformin in patients with contraindications or intolerance to metformin

Second-line options as add-on therapy to metformin in patients not achieving glycemic targets

Combination therapy components in dual, triple, or quadruple therapy regimens

Preferred options in patients at high risk of hypoglycemia, elderly patients, those with renal impairment, and when weight neutrality is desired

In patients with established atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease, guidelines prioritize agents with proven cardiovascular or renal benefits (GLP-1 receptor agonists and SGLT2 inhibitors) over DPP-4 inhibitors. However, DPP-4 inhibitors remain valuable options when first-line agents are contraindicated, not tolerated, or as components of combination therapy.

12.2 Patient Selection Criteria

Teneligliptin is particularly well-suited for specific patient populations:

Ideal Candidates:

Patients requiring glucose-lowering efficacy of -0.6% to -0.9% HbA1c reduction

Those at high risk for hypoglycemia (elderly, history of severe hypoglycemia, advanced CKD)

Patients with any degree of renal impairment including dialysis

Those preferring oral therapy over injectable agents

Patients requiring weight-neutral therapy

Those with polypharmacy who would benefit from low drug interaction potential

Patients intolerant to metformin or other first-line agents

Less Optimal Candidates:

Patients requiring maximal glucose-lowering (>1.5% HbA1c reduction needed)

Those with established ASCVD, heart failure, or CKD who would benefit from SGLT2 inhibitors or GLP-1 receptor agonists with proven cardiovascular/renal benefits

Patients prioritizing weight loss as a treatment goal

Those with a history of pancreatitis (relative contraindication requiring careful assessment)

12.3 Regional Practice Variations

Clinical practice patterns and regulatory approvals vary across regions:

Japan: Teneligliptin is widely used and integrated into treatment algorithms; approved for monotherapy and combinations

India: Increasingly utilized as cost-effective DPP-4 inhibitor option; extensive real-world experience

South Korea: Approved and used in clinical practice with favorable reimbursement

Western countries: Not yet approved in Europe, USA, or Canada; regulatory submissions under consideration

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Regional variations in prescribing reflect local regulatory approvals, formulary status, drug pricing, reimbursement policies, and clinical practice preferences. Where available, teneligliptin usage has grown steadily, reflecting acceptance by clinicians and patients.

XIII. PATIENT EDUCATION AND COUNSELING

13.1 Medication Information for Patients

Comprehensive patient education enhances treatment adherence and outcomes. Key counseling points for patients initiating teneligliptin include:

Dosing Instructions:

Take one tablet (20 mg) once daily, at approximately the same time each day

Can be taken with or without food, based on convenience

If a dose is missed, take it as soon as remembered unless it is almost time for the next dose; do not double doses

Expected Benefits:

Helps lower blood sugar levels by increasing natural hormones that help control blood sugar

May take several weeks to see full effect on blood glucose; HbA1c improvement assessed at 3 months

Works throughout the day to control both fasting and after-meal blood sugar

Low risk of causing low blood sugar when used alone or with metformin

Potential Side Effects:

Most people tolerate the medication well

Common side effects (if they occur) may include cold symptoms, constipation, or headache

Low blood sugar is rare unless combined with insulin or sulfonylureas

Contact healthcare provider if experiencing severe stomach pain, signs of allergic reaction, or unusual symptoms

Monitoring:

Continue regular blood sugar monitoring as recommended by healthcare provider

HbA1c testing every 3-6 months to assess effectiveness

Maintain healthy diet and exercise as essential components of diabetes management

Keep all scheduled appointments for diabetes care

13.2 Lifestyle Integration

Patients should understand that teneligliptin is one component of comprehensive diabetes management:

Diet: Maintain healthy eating patterns; no specific dietary restrictions required with teneligliptin

Exercise: Continue regular physical activity; medication does not increase exercise-related hypoglycemia risk

Weight management: Medication does not cause weight gain, supporting weight management efforts

Sick day management: Continue taking medication during illness unless unable to eat or drink; contact provider if concerns

13.3 When to Contact Healthcare Provider

Patients should be instructed to contact their healthcare provider if:

Blood sugar remains high (>300 mg/dL) despite medication

Experiencing symptoms of severe low blood sugar (unlikely but possible if on combination therapy)

XIV. FUTURE PERSPECTIVES AND ONGOING RESEARCH

14.1 Expanding Clinical Applications

Ongoing and planned research continues to explore teneligliptin's potential in various clinical contexts:

Cardiovascular Outcomes: While dedicated cardiovascular outcomes trials for teneligliptin have not been completed, registry-based studies and prospective cohort studies are ongoing to further

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characterize cardiovascular safety and potential benefits. Mechanistic studies evaluating effects on endothelial function, arterial stiffness, oxidative stress, and inflammation may provide insights into cardiovascular effects beyond glucose lowering.

Renal Outcomes: Given the growing recognition of diabetes-related kidney disease as a major health burden, studies evaluating teneligliptin's effects on renal endpoints including albuminuria progression, eGFR decline, and hard renal outcomes are of interest. Preclinical data suggesting potential renoprotective effects through anti-inflammatory and anti-fibrotic mechanisms warrant clinical investigation.

Beta-Cell Preservation: Long-term studies evaluating whether chronic DPP-4 inhibition preserves beta-cell function and delays diabetes progression would be valuable. While current evidence suggests improvements in insulin secretory capacity, definitive demonstration of disease modification requires extended follow-up with appropriate endpoints.

14.2 Novel Combination Therapies

Research continues to evaluate teneligliptin in novel combination regimens:

Triple Combinations: Studies are evaluating teneligliptin as a component of triple therapy with metformin plus SGLT2 inhibitors or metformin plus GLP-1 receptor agonists. Preliminary data suggest complementary mechanisms may provide additive glucose-lowering effects, though clinical benefit beyond dual therapy requires confirmation.

Fixed-Dose Combinations: Development of fixed-dose combination products combining teneligliptin with metformin or other agents may improve adherence through pill burden reduction. Such formulations are under development or approved in select markets.

Insulin Combinations: Further research on optimal strategies for combining teneligliptin with various insulin regimens (basal, prandial, premixed) may help define best practices for treatment intensification.

14.3 Precision Medicine Approaches

Emerging research explores whether genetic, metabolic, or clinical biomarkers can identify patients most likely to respond to teneligliptin:

Pharmacogenomics: Studies evaluating genetic variants in DPP-4, incretin receptors, or drugmetabolizing enzymes may identify subgroups with enhanced or reduced response to therapy.

Metabolic Phenotyping: Research characterizing patients based on predominant pathophysiologic defects (insulin resistance vs. insulin deficiency, incretin effect magnitude) may enable precision targeting of therapies to individual patient profiles.

Biomarker-Guided Therapy: Identification of baseline or early-response biomarkers predicting longer-term outcomes could enable personalized treatment selection and intensification strategies.

14.4 Novel Drug Delivery Systems

Research into alternative formulations and delivery systems may expand teneligliptin's applications:

Extended-Release Formulations: Development of modified-release formulations providing more consistent drug levels may optimize pharmacodynamic effects.

Combination Delivery Systems: Novel formulations enabling co-delivery with complementary agents through integrated delivery platforms may improve adherence and outcomes.

14.5 Mechanistic Research

Ongoing basic and translational research continues to elucidate teneligliptin's effects beyond glucose lowering:

Anti-Inflammatory Effects: Studies evaluating effects on inflammatory markers, cytokines, and immune cell function may reveal immunomodulatory effects relevant to diabetes complications.

Effects on Other DPP-4 Substrates: Research characterizing effects on non-incretin DPP-4 substrates including neuropeptide Y, substance P, and chemokines may reveal additional biological effects.

Organ-Specific Effects: Tissue-level studies evaluating effects in heart, kidney, brain, and other organs may identify mechanisms underlying clinical effects and potential new applications.

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XV. CONCLUSIONS

Teneligliptin represents a valuable addition to the therapeutic armamentarium for type 2 diabetes mellitus, offering a distinctive profile within the DPP-4 inhibitor class characterized by potent and sustained enzyme inhibition, balanced elimination through multiple pathways, and lack of dose adjustment requirements in renal or hepatic impairment. These pharmacokinetic advantages translate into practical clinical benefits including simplified prescribing, reduced medication error risk, and broad applicability across diverse patient populations including those with significant comorbidities.

Clinical trial evidence and real-world experience demonstrate that teneligliptin effectively reduces HbA1c levels by 0.6-0.9%, improves fasting and postprandial glucose control, and can be used as monotherapy or in combination with most other antidiabetic agents. The glucose-dependent mechanism of action confers important safety advantages including low hypoglycemia risk, weight neutrality, and good overall tolerability. The ability to use teneligliptin without dose adjustment in patients with any degree of renal impairment, including those on dialysis, addresses a significant unmet need in a high-risk population with limited treatment options.

While teneligliptin has not undergone dedicated cardiovascular outcomes trials, available evidence suggests cardiovascular safety, and the agent fits appropriately within contemporary treatment algorithms as a second-line or later option for patients not achieving glycemic targets on initial therapy or as an alternative first-line agent in patients with contraindications to metformin. The drug is particularly well-suited for elderly patients, those with renal impairment, patients at high hypoglycemia risk, and those requiring weight-neutral therapy.

Real-world studies validate clinical trial findings and demonstrate that teneligliptin's efficacy and safety profiles translate effectively to routine clinical practice, with high treatment persistence and satisfaction rates supporting long-term utility. The favorable benefit-risk profile, convenient oncedaily dosing, low interaction potential, and applicability in special populations position teneligliptin as a clinically useful option for individualized T2DM management.

Future research will continue to define teneligliptin's role in precision medicine approaches, evaluate potential benefits beyond glucose lowering, and explore novel applications and combinations. As our understanding of teneligliptin's multifaceted effects continues to evolve, this agent will remain a valuable therapeutic option contributing to comprehensive, patient-centered diabetes care.

In summary, teneligliptin exemplifies contemporary diabetes pharmacotherapy characterized by targeted mechanism of action, favorable safety profile, and practical clinical advantages. For appropriate patient populations, teneligliptin represents an effective, safe, and convenient treatment option supporting achievement and maintenance of glycemic goals as part of comprehensive diabetes management strategies.

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