INTRA LIFE

Tenisug-M-500/1000®

Teneligliptin 20mg + Metformin Hydrochloride 500mg / 1000mg (Prolonged Release) Tablet

WIN THE WAR

AGAINST DIABETES

WITH THE AFFORDABLE GLIPTIN & METFORMIN

Introduction

Diabetes is a common non communicable disease and has reached to epidemic stage in many countries. Globally, 415 million people are living with diabetes and this leading cause of death. This number is expected to rise to 642 million by 2040. Annually, nearly 5 million were dead with diabetes. The 3 populous countries of China, India, the US, and the Russian Federation reported highest deaths due to diabetes.

Diabetes affects many organs, and complications due to high blood glucose are an important cause of disability, reduced quality of life and premature death.[1] In 2015, globally, 5 million people aged between 20 years and 79 years died due to diabetes; this accounts for one death every 6 seconds.[1]

Diabetes is a chronic disease that requires lifelong medical care and attention for multiple risk reduction and treatment approach beyond glycemic control.[2] Treatment objectives must be the prevention of long-term and long-term complications associated with diabetes.[2] Additionally, patient education and support are important aspects.[2] This will improve patient outcomes.[2] A multidisciplinary approach is required for the management of diabetes.[2]

Considering the large epidemic of type 2 diabetes mellitus (T2DM), newer therapies that improve efficacy, tolerability, and long-term compliance and prevent complications associated with T2DM are always required and preferred.[3] Recently, a newer oral active glycosylated peptidyl peptidase 4 (DPP-4) inhibitor, teneligliptin, has been made available in some countries such as Japan, Argentina and India.[3] This review highlights the clinical importance of teneligliptin in the management of T2DM.

Role of DPP-4 inhibitors in the management of T2DM

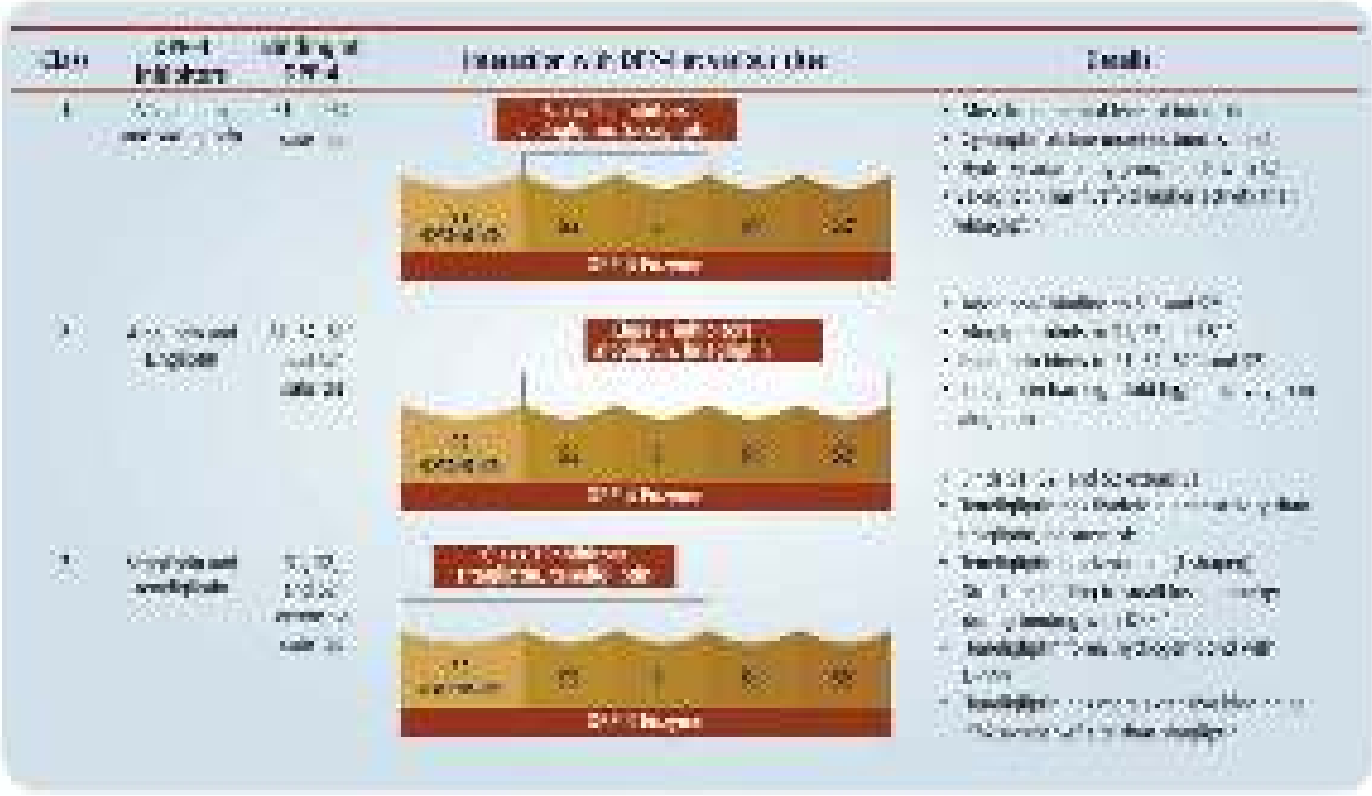
DPP-4 inhibitors are recommended as monotherapy or in double and triple drug combination with other oral glucose lowering agents such as metformin, sulfonylureas, thiazolidinediones, or even with insulin.[4] As a class, DPP-4 inhibitors are considered as a cornerstone in the management of T2DM due to their efficacy, favourable tolerability profile such as low risk of hypoglycemia and weight gain, and convenience in once-a-day dosage.[4]

Currently, eight DPP-4 inhibitors, namely alogliptin, anagliptin, gemigliptin, linagliptin, saxagliptin, sitagliptin, teneligliptin, and vildagliptin, are available for the management of T2DM.[4] All these DPP-4 inhibitors have similar mechanism of action and safety profile. In spite of their similar mechanism of action, DPP-4 inhibitors differ in some important pharmacokinetic and pharmacodynamic parameters, which may have clinical significance in real-life scenario.

Are All DPP-4 Inhibitors Same?

Binding modes of DPP-4 inhibitors with the active site of DPP-4 enzyme.[4] DPP-4 enzyme has five binding sites (subsites), namely, S1, S2, S1′, S2′, and S2 extensive (Figure 2).[4] An interaction of DPP-4 inhibitors with S1′ and S2 is considered to be the fundamental interaction that is required for DPP-4 inhibition.[5] Additional interaction with S1, S2, and S2 extensive site may further increase the DPP-4 inhibition.[5] DPP-4 inhibitors are classified according to the interactions with a DPP-4 enzyme (Table 1).[4] Classification of DPP-4 inhibitors is based on

their selectivity for enzyme and are Class 1, Class 2, and Class 3.[7] Class 1 inhibitors (eg, sitagliptin and saxagliptin) bind with S1 and S2 and are considered as fundamental/basic inhibitors.[7] Class 2 inhibitors (vildagliptin and linagliptin) bind to the additional sites of S1 and S2' and may produce more DPP-4 inhibition than Class 1.[7] Class 3 inhibitors (alogliptin and teneligliptin) bind additional site of S2 extensive and produce more extensive DPP-4 inhibition.[8] Teneligliptin, a Class 3 inhibitor reported five to eight times more potent than other gliptins.[8]



Teneligliptin

Teneligliptin is a novel oral DPP-4 inhibitor and has a unique structure consisting of two consecutive rings[9]. Due to this unique structure, teneligliptin binds to S2 extensive subsite of DPP-4, which in turn enhances its potency and selectivity.

Reported evidence suggests that with teneligliptin 20 mg therapy, Tmax was 1 hour and t1/2 was 18.9 hours. Maximum 89.7% inhibition in plasma DPP-4 activity was noted within 2 hours and maintained >80% at 24 hours. Compared to pre-dose, active plasma GLP-1 concentration was higher throughout the day and even at 24 hours after administration of teneligliptin 20 mg. Metabolism of teneligliptin was mainly mediated through CYP3A4, a cytochrome P450 isozyme, and flavin-containing monooxygenases (FMO1 and FMO3).[10]

A weak inhibitory activity of teneligliptin on CYP2D6, CYP3A4, and FMO was noted, while there was no inhibitory activity on CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C8/9, CYP2C19, and CYP2E1. There was no induction of expression of CYP1A2 or CYP3A4.

Reported evidence suggests that teneligliptin is metabolized and eliminated via both renal and hepatic routes. Approximately 34% of teneligliptin is excreted unchanged via the renal route, while 66% is metabolized and eliminated via hepatic and biliary routes.[11]

Effects of teneligliptin on 24-hour blood glucose control

A 4-week, randomized, double-blind, placebo-controlled, parallel-group study was conducted to analyse the pharmacokinetic and pharmacodynamic characteristics, effects on blood glucose control over 24 hours, and safety of once-daily teneligliptin in patients with T2DM inadequately controlled with diet and exercise. A total of 96 subjects, which included 32, 34, and 33 subjects in placebo, teneligliptin 10 mg group, and teneligliptin 20 mg group, respectively, were randomized and analyzed. Plasma concentration of teneligliptin was maintained for 24 hours; similarly, ≥ 90% inhibition of DPP-4 was noted at 24 hours of administration.

Compared to the placebo group, significantly lower 2-hour postprandial glucose (2-hour PPG), 24-hour mean glucose, and fasting plasma glucose (FPG) were noted in teneligliptin (10/20 mg tested) groups. Teneligliptin 10 mg exhibited mean reduction in 2-hour PPG after each meal as compared to placebo. Compared to placebo, a mean difference of −52.7 mg/dL, −34.8 mg/dL, and −37.5 mg/dL was noted ($P < 0.001$) for all the 2-hour PPG after breakfast, lunch, and dinner, respectively, in teneligliptin 10 mg group. Similarly, mean difference in reduction of 2-hour PPG after breakfast, lunch, and dinner was −38.1 mg/dL ($P < 0.001$), −20.6 mg/dL ($P = 0.21$), and −16.1 mg/dL ($P = 0.008$), respectively, with teneligliptin 20 mg compared to placebo. No potential glucose active glucagon-like peptide-1 concentrations were also increased with teneligliptin 10/20 mg compared to placebo. A similar incidence of adverse events (AEs) was noted in all groups with no incidence of serious AE including hypoglycemia.[1]

Role of teneligliptin in patients with T2DM inadequately controlled with diet and exercise

Kadowaki et al. evaluated the efficacy, safety, and dose response relationship of teneligliptin in Japanese patients with T2DM and inadequately controlled with diet and exercise through a randomized, double-blind, placebo-controlled, parallel-group study for 12 weeks. A total of 324 Japanese T2DM patients with age 20–75 years, HbA1c 6.5%–10.5%, and not taking any oral anti-hyperglycemic agent for ≥ 8 weeks were randomized to receive teneligliptin 10 mg (n=84), 20 mg (n=79), 40 mg (n=81), and placebo (n=80) once daily for 12 weeks.

Significantly greater reductions in HbA1c and FPG were reported in all teneligliptin groups compared to placebo group. AEs were similar in all groups. There was no significant difference in the incidence of hypoglycemia among the four groups. Thus, in patients with T2DM inadequately controlled with diet and exercise, treatment with teneligliptin resulted a significant and clinically important reduction in glycemic parameters.[2]

The efficacy and safety of teneligliptin added to ongoing metformin monotherapy in patients with type 2 diabetes: a randomized study with open-label extension

The study investigated the efficacy and tolerability of teneligliptin co-administered to patients with type 2 diabetes mellitus (T2DM) who were inadequately controlled by stable metformin monotherapy (≥ 1000 mg/day). A total of 447 patients from 55 European centers who completed a 14-day screening and 14-day run-in phase received randomized, double-blind treatment with 5, 10, 20 or 40 mg teneligliptin or placebo once daily for 24 weeks. 364 patients continued treatment in a 28-week open-label extension during which they received teneligliptin 20 mg once daily. Co-administration of teneligliptin (5 to 40 mg) with metformin demonstrated dose-related and statistically significant reductions in HbA1c after 24 weeks (−0.18% to −0.61%) placebo-adjusted) of double-blind treatment. The greatest reduction in HbA1c was seen with teneligliptin at 40 mg (−0.63%) at Week 24. There was also a dose-dependent increase in proportion of responders achieving HbA1c < 7.0% at this endpoint. Responses were maintained throughout 28 weeks open-label treatment with 20 mg teneligliptin. Treatment was well tolerated to Week 52 and the overall incidence of hypoglycaemia during 52 weeks was 27.4%.

CONCLUSIONS: Teneligliptin coadministered with metformin produces significant reductions in HbA1c in patients with T2DM without the usual hypoglycemia.[7]

Teneligliptin real-world efficacy assessment of type 2 diabetes mellitus patients in India (TREAT-INDIA study)

Predesigned structured proforma was used for this audit to collect information from the prescribing physicians on the efficacy of teneligliptin when prescribed as either monotherapy or in combination with other antidiabetic drugs. Data collected were anonymized and information collected included demographic data, antidiabetic medications, and glycemic status of the patients at the time of initiation and after 3 months of teneligliptin therapy. Data were collected between September 2015 and December 2015. The glycemic efficacy was assessed by analyzing the mean change in values of glycosylated hemoglobin (HbA1c), FPG, and PPG from baseline following teneligliptin therapy. Data of 4803 patients was available for analysis. There was statistically significant improvement in mean HbA1c, FPG, and PPG with teneligliptin therapy. Mean changes in HbA1c, FPG, and PPG were −1.37% ± 1.15%, 31.39 ± 35.41 mg/dL, and 50.83 ± 54.27 mg/dL, respectively. Subgroup analysis revealed that HbA1c (%) reduction with teneligliptin when used as monotherapy, add-on to metformin or add on to metformin plus sulfonylureas combination, add on to metformin plus alpha glucosidase inhibitor combination in patients at baseline was 0.98 ± 0.55, 1.07 ± 0.53, 1.46 ± 1.33, 1.43 ± 0.82, and 1.35 ± 1.10, respectively.

Real-world data suggests that teneligliptin significantly improves glycemic control in Indian patients with T2DM when prescribed either as monotherapy or as an add-on to one or more other commonly prescribed antidiabetic drugs.[7]

Summary

1. Globally, prevalence of diabetes has reached an alarming stage with 415 million patients. This has a huge burden on public health system and prompt intervention is required to reduce serious short-term and long-term complications associated with diabetes. In this situation, the addition of newer and effective medicines is always welcomed.
2. Teneligliptin is a novel DPP-4 inhibitor and has a unique structure and binds to S1, S2, and S2 extensive subsite of DPP-4 enzyme leading to enhanced potency and selectivity.
3. Teneligliptin significantly reduces fasting glucose with a reduction of HbA1c of 0.8%–0.9% in 12 weeks, which was maintained up to 52 weeks of teneligliptin therapy.
4. Teneligliptin reported favorable tolerability with low AEs and a weight neutral. No dose adjustment is required in patients with any degree of renal impairment or ESRD and even in mild to moderate hepatic impairment. These are some unique and novel properties of teneligliptin.

References

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Tenisug-M-500/1000™

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Indications :

In patients who have not sufficiently responded to either of the following treatments:
a) Diet and/or exercise therapy alone. b) Use of sulfonylureas in addition to diet and/or exercise therapy
c) Use of thiazolidinediones in addition to diet and/or exercise therapy

Dosage :

The usual adult dosage is 20 mg of teneligliptin administered orally once daily. If efficacy is insufficient, the dose may be increased up to 40 mg once daily while closely monitoring the clinical course.

Now Available

Tenisug-20™

Teneligliptin 20mg Tab

INTRALIFE

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