PRODUCT MONOGRAPH

TENEPAN-M 500

Teneligliptin 20 mg / Metformin Hydrochloride ER 500 mg

TENEPAN-M 1000

Teneligliptin 20 mg / Metformin Hydrochloride ER 1000 mg

For Oral Administration

Anti-diabetic Agent (DPP – 4 Inhibitor and Biguanide)

Manufactured By:

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Date of Preparation:

24-07-2019

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TENEPAN-M 500 & TENEPAN-M 1000

(Teneligliptin Hydrobromide Hydrate and Metformin Hydrochloride Extended-Release Tablets)

For Oral Administration

ANTIDIABETIC AGENT (DPP – 4 Inhibitor and Biguanide)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	**Dosage Form / Strength**	**Approved Indications**
Oral	TENEPAN-M 500 Each Tablet Contain: Teneligliptin 20 mg Hydrobromide Hydrate and Metformin Hydrochloride Extended-release 500 mg. TENEPAN-M 1000 Each Tablet Contain: Teneligliptin 20 mg Hydrobromide Hydrate and Metformin Hydrochloride Extended-release 1000 mg	Indicated in patients with T2DM whose diabetes is not adequately controlled on Metformin or Teneligliptin alone or who are already treated with the combination of Teneligliptin and Metformin, as separate tablets.

INDICATIONS AND CLINICAL USE

INDICATIONS:

Tenepan-M 500 & **1000** is indicated in patients with T2DM whose diabetes is not adequately controlled on Metformin or Teneligliptin alone or who are already treated with the combination of Teneligliptin and Metformin, as separate tablets.

CONTRAINDICATIONS

Patients having known history of hypersensitivity to Teneligliptin, Metformin or to any excipients of the formulation.

Patients having severe ketoacidosis, diabetic coma or pre-coma and Type 1 DM (since a prompt correction of hyperglycemia is required by transfusion and insulin, the administration of Teneligliptin and Metformin tablet is not suitable).

Patients having severe infection, perioperative, severe trauma and severe external injury, since in these cases glycemic control is desired by insulin injection, therefore the administration of Teneligliptin and Metformin tablet is not suitable.

Tenepan-M 500 and Tenepan-M 1000 is contraindicated in patients with a history of lactic acidosis, irrespective of precipitating factors. In excessive alcohol intake, acute or chronic and patients suffering from severe dehydration. Tenepan-M is contraindicated during pregnancy and breastfeeding.

WARNINGS AND PRECAUTIONS

WARNINGS:

In allergic reaction, symptoms such as difficulty in breathing or swallowing, chest tightness, swelling, skin rashes, and hives.

The correct dosage and prescription commonly depend on the patient and the condition being treated. Kindly advise patients not to adjust their dosage without the approval from the health care professional. This product is only for use as prescribed and instructed.

Kindly instruct patients to engage in regular physical activity, and to follow a special diet.

PRECAUTIONS:

It is possible that hypoglycemia may occur in the patients. Kindly inform patients regarding sign and symptoms of hypoglycemia and in this condition what should the patient do to correct hypoglycemia.

Teneligliptin and Metformin should be given with precaution in conditions like pregnancy, breastfeeding, trying to conceive, using any other medication (prescription or non-prescription), using any herbal products or supplements, or having any allergies or other health problems.

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to Metformin accumulation during treatment with Tenepan-M 500 & Tenapan-M 1000.

ADVERSE REACTIONS

Teneligliptin

Adverse Drug Reaction Overview

The following adverse drug reactions have been identified in the clinical trials on Teneligliptin.

In clinical trials conducted in Japan, 232 adverse reactions to this drug (including abnormal laboratory tests) were reported in 156 patients (9.5%) of total 1645 patients. The most frequently observed adverse reactions were hypoglycemia in 43 patients (2.6%) and constipation in 14 patients (0.9%).

In a clinical study conducted in 237 Indian patients with Type 2 DM inadequately controlled on diet and exercise alone, a total of 158 patients were exposed to Teneligliptin Tablets for a mean duration of 106.7 days. Adverse events considered to be related to study medication were reported for 6/158 (3.8%) of patients in the Teneligliptin group. The most frequent individual adverse event was dizziness in Teneligliptin group (5/158) 3.2%, followed by headache in (5/158) 3.2%, diarrhea in (4/158) 2.5% and pyrexia in (4/158) 2.5%. An adverse event (cancer of right pyriform fossa) leading to early termination from the study was reported for 1/158 (0.6%) of patient in the Teneligliptin group, this was unrelated to the study drug. No serious adverse event related to the study drug was reported during the study. Most of the adverse events were mild in severity.

Other Adverse Reaction / Side Effects:

Table 1: Teneligliptin Adverse/ Side Effects

Incidence Types	0.1% - 1%	< 0.1%
Digestive system	Constipation, abdominal swelling, abdominal discomfort, nausea, stomach ache, flatulence, stomatitis, gastric polyp, colon polyp, duodenal ulcer, reflux esophagitis, diarrhea, anorexia, increased amylase, increased lipase, acute pancreatitis.	
Liver	Increased AST (SGOT), increased ALT (SGPT), and increased γ-GTP.	Rise in ALP
Kidney and urinary system	Albuminuria, positive ketone bodies in urine, increased uric acid in blood.	
Skin	Eczema, Wet rash, pruritus, allergic dermatitis	
Others	Increased CK (CPK), increased serum potassium, fatigue, allergic rhinitis, and increased serum uric acid.	

If adverse reactions are observed, then the drug administration should be discontinued and appropriate measures should be taken.

Metformin

Adverse Drug Reaction Overview

The following adverse drug reactions have been identified in the clinical trials on Metformin.

A 24 weeks randomized, double-blind, fixed-dose, phase III clinical trial was conducted in the U.S., a total of 178 patients received extended-release Metformin therapy and 174 patients received immediate-release Metformin. The most frequent adverse events thought to be related to extended-release metformin were diarrhea (14.2%), nausea (9.7%), dyspepsia (5.1%), and abdominal pain (5.1%) as compared to diarrhea (14.4%), nausea (10.9%), dyspepsia (5.7%), and abdominal pain (2.3%) in immediate-release Metformin.

During controlled clinical trials of 29 weeks duration, approximately 9% of patients on Metformin monotherapy and 6% of patients on Metformin /Sulfonylurea therapy developed asymptomatic subnormal serum vitamin B12 levels; serum folic acid levels did not decrease significantly. However, only five cases of megaloblastic anemia have been reported with Metformin administration (none during U.S. clinical studies) and no increased incidence of neuropathy has been observed.

In controlled clinical trials, the incidence of rash/dermatitis was comparable to placebo for Metformin monotherapy and to sulfonylurea for metformin /sulfonylurea therapy. Reports of skin reactions such as erythema, pruritus, and urticaria are very rare.

Table 2: Metformin other Adverse / Side Effects

Incidence Types	0.01% - 10%
Lactic Acidosis	very rare (<1/10, 000)
Digestive system	(>1/10) Diarrhea, nausea, vomiting, abdominal bloating, flatulence, and anorexia
Liver	very rare (<1/10,000 and isolated reports): Liver function tests abnormalities
Special Senses	common (≥1/100): During initiation of metformin therapy complaints of taste disturbance are common, i.e. metallic taste
Skin	very rare (<1/10,000) Eczema, Wet rash, pruritus, allergic dermatitis
Hematologic	subnormal serum vitamin B12 levels (≥1/10,000)

DRUG INTERACTIONS

Teneligliptin and other important Drug- Drug interactions:

Teneligliptin is metabolized mainly by CYP3A4 and flavin containing monoxygenase (FMO1 and FMO3), and urinary excretion rate of unaltered substance was 14.8% to 22.1%.

Teneligliptin Metformin Combination:

When a repeated dose of 40 mg Teneligliptin once daily for 8 days and a repeated combined dose (6 to 8th day of Teneligliptin administration) of 850 mg Metformin twice daily were administered to the healthy adults, the ratio (90% CI) of C_{max} of Teneligliptin and AUC_{0-24} hrs geometric minimum mean-square value was 0.907 (0.853 - 0.965) and 1.042 (0.997 - 1.089) with respect to repeated dose administration of Teneligliptin only. Furthermore, when a repeated combined dose (4th to 8th day of Metformin administration) of 850 mg Metformin twice daily for eight days and 40 mg Teneligliptin once daily was administered to the healthy adults, the ratio (90% CI) of C_{max} of Metformin and AUC_{0-12} hrs geometric minimum mean-square value was 1.057 (0.974 - 1.148) and 1.209 (1.143 - 1.278) with respect to repeated-dose administration of Metformin only, and the AUC_{0-12} hrs of Metformin increased to 20.9% due to co-administration.

Teneligliptin Glimepiride Combination:

When a repeated dose of 1 mg Glimepiride for 4 days and a single combined dose (2nd day of Glimepiride administration) of 40 mg Teneligliptin were administered to the healthy adults, the ratio (90% confidence interval [CI]) of C_{max} of Teneligliptin and $AUC_{0-\infty}$ geometric mean value was 0.971 (0.866- 1.088) and 0.926 (0.894 – 0.959) with respect to single-dose administration of Teneligliptin alone. Furthermore, when a repeated-dose of 40 mg Teneligliptin for seven days and a single combined dose (7th day of Teneligliptin administration) of 1 mg glimepiride were administered to the healthy adults, the ratio (90% CI) of C_{max} of Glimepiride and $AUC_{0-\infty}$ geometric mean value was 1.016 (0.932 – 1.106) and 1.023 (0.978 – 1.071) with respect to single-dose administration of Glimepiride alone.

Teneligliptin Pioglitazone Combination:

When a repeated dose of 30 mg Pioglitazone for 9 days and a single combined dose (7^{th} day of Pioglitazone administration) of 40 mg Teneligliptin were administered to the healthy adults, the ratio (90% CI) of C_{max} of Teneligliptin and $AUC_{0-\infty}$ geometric mean value was 1.117 (0.984 -1.266) and 1.005 (0.967 - 1.045) with respect to single-dose administration of Teneligliptin alone, and the C_{max} of Teneligliptin increased 11.7% due to co-administration. Furthermore, when a repeated-dose of 40 mg Teneligliptin for 9 days and a single combined dose (7^{th} day of Teneligliptin administration) of 30 mg Pioglitazone were administered to the healthy adults, the ratio (90% CI) of C_{max} of Pioglitazone and $AUC_{0-\infty}$ geometric mean value was 1.004 (0.917 - 1.100) and 1.134 (1.060 - 1.213) with respect to single-dose administration of Pioglitazone alone. Similarly, the ratio (90% CI) of C_{max} of active metabolites (M-III and M-IV) of Pioglitazone and $AUC_{0-\infty}$ geometric mean value was 1.041 (0.975 - 1.113) and 1.116 (1.056 - 1.180) in M-III and 1.028 (0.963 - 1.096) and 1.088 (1.032 - 1.147) in M-IV.

Teneligliptin Ketoconazole Combination:

When a repeated dose of 400 mg Ketoconazole for 6 days and a single combined dose (4th day of Ketoconazole administration) of 20 mg Teneligliptin were administered to the healthy adults, the ratio (90% CI) of C_{max} of Teneligliptin and AUC $_{0}$ - $_{\infty}$ geometric minimum mean-square value was 1.37 (1.25 - 1.50) and 1.49 (1.39 - 1.60) with respect to single-dose.

Table 3: Teneligliptin Drug- Drug Interaction

Drug Name	Clinical Condition/ Measures	Mechanism and Risk Factors
Medicines for Diabetes Fast-acting insulin secretagogue *Alpha* – glucosidase inhibitor Biguanide Thiazolidinediones GLP-1 analog preparation SGLT2 inhibitor Insulin preparation	Since hypoglycemia might occur, these drugs should be administered while carefully observing the patient's condition. Particularly, when co-administered with Sulfonylurea or Insulin formulation, there is a possibility of higher risk of hypoglycemia. In order to reduce the risk of hypoglycemia caused by Sulfonylurea or Insulin formulation, consider decreasing the quantity of Sulfonylurea or Insulin formulation. When hypoglycemia is observed, usually, cane sugar should be given, and when co-administered with Alpha-glucosidase inhibitor, glucose should be given.	Hypoglycemic action is increased.
Drugs increasing hypoglycemic action *Beta* – blocking agents Salicylic acid Monoamine oxidase inhibitor	Since the blood glucose may further decrease, these drugs should be administered while carefully observing the patient's condition in addition to blood glucose level.	Hypoglycemic action is increased.
Drugs decreasing hypoglycemic action Adrenalin adrenocortical hormone	Since the blood glucose may increase, these drugs should be administered while carefully observing the patient's condition in addition to blood glucose level.	Hypoglycemic action is decreased.
Drugs known to cause QT prolongation **Class IA antiarrhythmic drug** Quinidine sulfate hydrate, Procainamide hydrochloride **Class III antiarrhythmic drugs** Amiodarone hydrochloride, Sotalol hydrochloride	QT prolongation might occur.	QT prolongation is seen with single administration of these drugs.

Metformin and other important Drug- Drug interactions:

Metformin Glibenclamide Combination: In a single-dose interaction study in type 2 diabetes patients, co-administration of Metformin and Glibenclamide did not result in any changes in either Metformin pharmacokinetics or pharmacodynamics. Decreases in Glibenclamide AUC and C_{max} were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between Glibenclamide blood levels and pharmacodynamic effects make the clinical significance of this interaction uncertain.

Metformin Furosemide Combination: A single-dose, Metformin-Furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased the Metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in Metformin renal clearance. When administered with Metformin, the C_{max} and AUC of Furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in Furosemide renal clearance. No information is available about the interaction of Metformin and Furosemide when co-administered chronically.

Metformin Nifedipine Combination: A single-dose, Metformin-Nifedipine drug interaction study in normal healthy volunteers demonstrated that co-administration of Nifedipine increased plasma Metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of Metformin. Metformin had minimal effects on Nifedipine.

Metformin Cationic drugs Combination: Cationic drugs (e.g., Amiloride, Digoxin, Morphine, Procainamide, Quinidine, Quinine, Ranitidine, Triamterene, Trimethoprim, or Vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with Metformin by competing for common renal tubular transport systems. Such interaction between Metformin and oral Cimetidine has been observed in normal healthy volunteers in both single-dose and multiple-dose Metformin-Cimetidine drug interaction studies, with a 60% increase in peak Metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood Metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on Cimetidine pharmacokinetics.

Metformin Other drug combination: Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the Thiazides and other Diuretics, Corticosteroids, Phenothiazines, Thyroid products, Estrogens, Estrogen plus Progestogen, Oral Contraceptives, Phenytoin, Nicotinic acid, Sympathomimetics, Calcium channel blocking drugs, isoniazid and *Beta*-2-agonists. ACE-inhibitors may decrease the blood glucose levels.

Elimination rate of the anticoagulant Phenprocoumon has been reported to be increased by 20% when used concurrently with Metformin. Therefore, patients receiving Phenprocoumon or other anti-vitamin K anticoagulants should be monitored carefully when both types of drugs are used simultaneously.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Tenepan-M 500 & Tenepan-M 1000: 1) Patients inadequately controlled on either Teneligliptin or Metformin monotherapy. 2) Patients switching from combination therapy of Teneligliptin plus Metformin Extended Release as separate tablets. 3) Drug naïve patients with entry HbA1c ≥7.5 %. 4) In combination with other oral antidiabetic drug (OAD) (i.e. triple combination therapy) as an adjunct to diet and exercise in adult patients inadequately controlled with Metformin and other OAD. Do not exceed maximum recommended dose (Teneligliptin 40 mg / Metformin Extended-Release 2000 mg) once daily, and should be given with meals to reduce the GI side effects associated with Metformin. Tenepan-M 500 should not be used in patients with hepatic impairment and in severe renal impairment (eGFR <30 mL/min/1.73m^2) whereas, Tenepan-M 1000 should not be used in patients with hepatic impairment and moderate to severe renal impairment (eGFR <60 mL/min/1.73m^2).

Administration

Tenepan-M 500 and Tenepan-M 1000 tablets must be swallowed with sufficient amount of water (approx. ½ glass), without chewing.

Missed Dose

The missed dose should be taken as soon as possible, unless it is almost time for the next dose. The patient should be advised not to take two doses at the same time.

DOSAGE RECOMMENDATION OF TENEPAN-M 500 and TENEPAN-M 1000 IN HEPATIC AND RENAL FAILURE:

Renal Failure

TENEPAN-M 500 should not be used in patients with moderate to severe renal impairment (eGFR <30 mL/min/1.73m^2) whereas, TENEPAN-M 1000 should not be used in patients with moderate to severe renal impairment (eGFR <60 mL/min/1.73m^2).

Table 4: Dosage Recommendation of Metformin in Renal Failure:

PROPOSED RECOMMENDATION FOR USE OF METFORMIN BASED ON eGFR			
Stage of Renal Failure	**eGFR Level (mL/min per 1.73m^2**	**Monitoring**	**Recommended Dose**
Normal	No renal impairment	No renal contraindication to Metformin	Upto 2550 mg
Mild	≥ 60 mL/min	No renal contraindication to Metformin Monitor renal function annually	≤1700 mg
Moderate	≥ 45 to 60 mL/min	Continue use Monitoring of renal function every 3 - 6 months	≤ 850 mg
Moderate	≧ 30 to 45 mL/min	Prescribe Metformin with caution Use lower dose (e.g. 50%, or half maximal dose) Monitor renal function every 3 months) Do not start new patients on Metformin	≤850 mg
Severe	≤ 30 mL/min	Stop Metformin	Not Recommended

eGFR (estimated Glomerular Filtration Rate): The "eGFR" is an estimated value derived from a measured serum creatinine, calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation:

GFR = $141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age}$ [if male]

GFR = $141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female]

S_{cr} is serum creatinine in mg/dL,κ is 0.7 for females and 0.9 for males,α is -0.329 for females and -0.411 for males,min indicates the minimum of S_{cr}/κ or 1, and max indicates the maximum of S_{cr}/κ or 1.

NOTE: eGFR to be calculated by online eGFR calculator- https://www.davita.com/gfr-calculator/

Table 5: USE OF TENEPAN-M 500 & TENEPAN-M 1000 IN RENAL FAILURE BASED ON PROPOSED RECOMMENDED METFORMIN DOSE

USE OF TENEPAN-M 500 & TENEPAN-M 1000 IN RENAL FAILURE BASED ON PROPOSED RECOMMENDED METFORMIN DOSE				
Stage of Renal Failure	**eGFR Level (mL/min per 1.73m^2**	**Monitoring**	**Metformin Recommended Dose**	**Tenepan-M Recommended Dose**
Normal	No renal impairment	No renal contraindication to Metformin	Upto 2550 mg	Tenepan-M 500 and Tenepan-M 1000
Mild	≥ 60 mL/min	No renal contraindication to Metformin Monitor renal function annually	≤1700 mg	Tenepan-M 500 and Tenepan-M 1000
Moderate	≥ 45 to 60 mL/min	Continue use Monitoring of renal function every 3 - 6 months	≤ 850 mg	Tenepan-M 500
Moderate	≧ 30 to 45 mL/min	Prescribe Metformin with caution Use lower dose (e.g. 50%, or half maximal dose) Monitor renal function every 3 months) Do not start new patients on Metformin	≤850 mg	Tenepan-M 500
Severe	≤ 30 mL/min	Stop Metformin	Not Recommended	Not Recommended

eGFR (estimated Glomerular Filtration Rate): The "eGFR" is an estimated value derived from a measured serum creatinine, calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation:

GFR = $141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age}$ [if male]

GFR = $141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female]

S_{cr} is serum creatinine in mg/dL,κ is 0.7 for females and 0.9 for males,α is -0.329 for females and -0.411 for males,min indicates the minimum of S_{cr}/κ or 1, and max indicates the maximum of S_{cr}/κ or 1.

NOTE: eGFR to be calculated by online eGFR calculator- https://www.davita.com/gfr-calculator/

Hepatic Failure

Tenepan-M 500 and Tenepan-M 1000 should not be used in patients with clinical or laboratory evidence of hepatic failure disease.

OVERDOSAGE

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy if required.

ACTION AND CLINICAL PHARMACOLOGY

CLINICAL PHARMACOLOGY

Teneligliptin

Mechanism of Action

The glucagon-like peptide-1 (GLP-1) is secreted from alimentary canal, in response to meal. This promotes insulin secretion from pancreas and regulates blood glucose post meal by controlling glucagon secretion. Teneligliptin exhibits a hypoglycemic effect by controlling the degradation of GLP-1 by inhibiting dipeptidyl peptidase-4 (DPP-4) activity. Thus increases blood concentration of active GLP-1.

Pharmacodynamics

DPP – 4 Inhibitory Actions and GLP – 1 Degradation Inhibitory Action:

1. Teneligliptin, inhibits concentration-dependent human plasma DPP-4 activity, and its IC_{50} value (95% CI) was 1.75 (1.62 - 1.89) nmol/L (in vitro).

2. Teneligliptin concentration-dependently suppressed the degradation of GLP-1 in rat plasma, with IC_{50} values and its 95% CI being 2.92nmol/L [2.21, 3.87] (in vitro).

3. In the glucose tolerance test using Zucker Fatty rats, an obesity model showing insulin resistance and abnormal glucose tolerance, Teneligliptin increased plasma active form GLP-1 concentration and plasma insulin concentration by its single-dose administration.

4. In patients having Type 2 DM, the administration of 20 mg Teneligliptin once daily inhibited the plasma DPP-4 activity and increased the plasma active form GLP-1 concentration.

Glucose Tolerance Improvement Action:

1. In the glucose tolerance test using Zucker Fatty rats, an obesity model showing insulin resistance and abnormal glucose tolerance, Teneligliptin controlled an increase in the blood glucose level by its single-dose administration.

2. In patients having Type 2 Diabetes Mellitus, the administration of 20 mg Teneligliptin once daily improved the blood glucose levels after breakfast, lunch, dinner and the fasting blood glucose levels.

Pharmacokinetics

Absorption:

Plasma Concentration:

1. **Single Dose Administration:**

The plasma concentration changes and the pharmacokinetic parameters of Teneligliptin after a single oral dose of 20 mg and 40 mg given on empty stomach to the healthy adults are shown below.

Pharmacokinetic parameters at the time of single dose

Oral drug administration in healthy adults.

Strengths	C_{max} (ng/mL)	AUC_{0-inf} (ng.hr/ml)	T_{max} (hr)	$T_{1/2}$ (hr)
20 mg	187.20±44.70	2028.9±459.5	1.8 (1.0-2.0)	24.2±5.0
40 mg	382.40±89.83	3705.0±787.0	1.0 (0.5-3.0)	20.8±3.2

n=6, Mean Value ± SD, T_{max}=Central value (minimum value - maximum value)

2. Repeated – Dose Administration:

The pharmacokinetic parameters of Teneligliptin after a repeated dose of 20 mg of Teneligliptin once daily for 7 days given 30 minutes before breakfast to the healthy adults are shown below. The state of equilibrium will be attained within 7 days.

Pharmacokinetic parameters at the time of repeated dose

Oral drug administration in healthy adults.

Dose	C_{max} (ng/mL)	AUC_{0-24} (ng.hr/ml)	AUC_{0-inf} (ng.hr/ml)	T_{max} (hr)	$T_{1/2}$ (hr)
After First dose	160.60±47.26	1057.2±283.9	1627.9±427.8	1.0 (0.4-2.0)	25.8±4.9
7 days after administration	220.14±59.86	1514.6±370.5	2641.4±594.7	1.0 (1.0-1.0)	30.2±6.9

n=7, Mean Value ± SD, T_{max}=Central value (minimum value - maximum value)

3. Foods Effect:

C_{max} decreased after a single dose of 20 mg of Teneligliptin given post meal to the healthy adults as compared to empty stomach and T_{max} prolonged from 1.1 hr to 2.6 hr; however, no difference observed in AUC

Pharmacokinetic parameters at the time of fasting and after food intake in healthy adults.

	C_{max} (ng/mL)	AUC_{0-24} (ng.hr/ml)	AUC_{0-inf} (ng.hr/ml)	T_{max} (hr)	$T_{1/2}$ (hr)
After First dose	232. 2 (236.2±43.77)	1855.5 (1861.1±148.1	2090.3 (2094.6±1 38.5)	1.1±0.4 26.5	26.5 (27.8±9.3)
7 days after administration	184.9 (187.5±33.55)	1806 (1814.6±183.3)	2044.0 (2056.1±230.9)	2.6±1.1 26.9	26.9 (28.3±9.5)

n=14, Geometric mean (Arithmetic mean value ± Standard Deviation). T_{max} = Arithmetic mean value ± Standard Deviation.

Rate of Protein Binding

The protein binding ratio was 77.6% to 82.2 % when the [^{14}C] label Teneligliptin (20, 100 and 500 ng/mL) was added to human plasma (in vitro).

Metabolism:

1. Following a single administration of 20 mg [^{14}C] label Teneligliptin to the healthy adults, the unaltered substance and the metabolites M1, M2, M3, M4, and M5 with respect to AUC $_{0\text{-inf}}$ calculated from the plasma radioactive concentration up to 72 hours after administration was 71.1%, 14.7%, 1.3%, 0.3% and 1.1% respectively.
2. Mainly, CYP3A4 and flavin-containing monooxygenases (FMO1 and FMO3) participate in the metabolism of Teneligliptin. Furthermore, although it showed a weak inhibitory action towards CYP2D6, CYP3A4, and FMO (IC_{50} value: 489.4, 197.5, and 467.2µmol/L respectively), it did not showed inhibitory action towards CYP1A2, CYP2A6,CYP2B6, CYP2C8, CYP2C8/9, CYP2C19, and CYP2E1; and CY P1A2 and CYP3A4 were not introduced (in vitro).

Excretion:

1. When a single oral dose of 20 mg and 40 mg Teneligliptin was given to the healthy adults on empty stomach, about 21.01% to 22.1% of dose was excreted as unaltered substance in urine, and the renal clearance was 37 to 39 mL/hr/kg.
2. When single oral dose of 20 mg [^{14}C] label Teneligliptin was given to the healthy adults, 45.4% of dosage radioactivity was excreted in urine and 46.5% was excreted in faeces up to 216 hours after administration. Furthermore, with respect to the dosage up to 120 hours after administration, the accumulated urinary excretion rate of unaltered substance, M1, M2, and M3 was 14.8%, 17.7%, 1.4%, and 1.9%, respectively and the accumulated faeces excretion rate of unaltered substance, M1, M3, M4, and M5 was 26.1%, 4.0%, 1.6%,0.3%, and 1.3%, respectively.
3. Teneligliptin is a substrate of P-glycoprotein that inhibited the transportation of digoxin up to 42.5% through P-glycoprotein in the concentration of 99 µmol/L. Furthermore, it showed a weak inhibitory action towards the Organic Anion Transporter 3(OAT 3) appeared in kidney, (IC $_{50}$ value: 99.2µmol/L); however, it did not showed inhibitory action towards OAT 1 and Organic Cation Transporter OCT2 (in vitro).

Renal Dysfunction:

When a single oral dose of 20 mg Teneligliptin was given to the renal dysfunction patients, no remarkable change was observed in C_{max} and $t_{1/2}$ depending on the extent/degree of renal dysfunction. On the other hand, in the mild renal dysfunction patients (Ccr≥ 50 to ≤ 80ml/min), moderate renal dysfunction patients (Ccr≥ 30 to ≤ 50ml/min) and severe renal dysfunction patient (Ccr<30ml/min), the AUC $_{0\text{-inf}}$ was found to be about 1.25 times, 1.68 times, and 1.49 times, respectively, as compared to the healthy adults. $AUC_{0\text{-}43hr}$ of terminal renal failure affected individual was about 1.16 times as compared to the healthy adults. Furthermore, 15.6% of Teneligliptin dose was removed due to haemodialysis.

Liver Dysfunction:

When a single oral dose of 20 mg Teneligliptin was given to the hepatic dysfunction patients, the C_{max} of Teneligliptin was found to be about 1.25 times and 1.38 times and $AUC_{0\text{-}inf}$ was about 1.46 times and 1.59 times, respectively, in slight hepatic dysfunction patient (total score 5-6 by Child - Pugh Classification) and moderate hepatic dysfunction patient (total score 7 – 9 by Child - Pugh Classification) as compared to the healthy adults.

Note: There was no clinical experience in high degree hepatic dysfunction patients (total score more than 9 by Child – Pugh Classification).

Pharmacokinetics in Elderly Patients:

When a single oral dose of 20 mg Teneligliptin was given to the healthy elderly patients (≥ 65 years old ≤ 75 years old, 12 patients) and non-elderly patients (≥ 45 years old ≤ 65 years old, 12 patients) on empty stomach, the ratio (90% CI) of geometric minimum mean-square value of elderly patient with C_{max} , $AUC_{0\text{-}inf}$, and $t_{1/2}$ of non-elderly patient was almost similar, 1.006 (0.871- 1.163) , 1.090 (0.975 - 1.218), and 1.054 (0.911- 1.219), respectively.

Metformin

Mechanism of Action

Metformin is an anti-hyperglycemic agent, which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin is a biguanide derivative producing an anti-hyperglycemic effect which is observed in diabetic patients or in diabetic animals. Its pharmacologic mechanisms of action are different from other classes of oral anti-hyperglycemic agents. Metformin may decrease hepatic glucose production, decrease intestinal absorption of glucose, and improve insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike Sulfonylureas, Metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects and does not cause hyperinsulinemia. With Metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

Pharmacodynamics

Metformin molecular mechanisms underlying action appear to be complex and remain a topic of considerable debate. However, there is general agreement that the administration of Metformin results in the phosphorylation and activation of AMP-activated protein kinase (AMPK) in the liver, which in turn may lead to diverse pharmacologic effects, including inhibition of glucose and lipid synthesis. Although the specific route of AMPK phosphorylation is not yet clear, the molecular components LKB1/STK11 and ATM have been shown to play a role in the phosphorylation of AMPK in the presence of Metformin. However, ATM, LKB1, and AMPK are not the direct targets of Metformin. A recent study

using liver-specific AMPK-knockout mice has shown that inhibition of hepatic glucose production by Metformin is preserved, suggesting that Metformin may inhibit hepatic gluconeogenesis in an LKB1-independent and AMPK-independent manner.

The findings from this study are yet to be replicated, and therefore, the role of AMP kinase in the inhibition of gluconeogenesis can still be considered. In a separate study in *Oct-1*-knockout mice, Metformin both activated AMPK and reduced gluconeogenesis. A separate group has also concluded that Metformin inhibits hepatic gluconeogenesis through AMPK-dependent regulation of SHP. Therefore, a reduction in gluconeogenesis may occur both ways, in an AMPK-dependent and an AMPK-independent manner.

Although the direct target is not fully elucidated, Metformin specifically inhibits complex I of the mitochondrial respiratory chain, suggesting that this inhibition may activate AMPK by increasing the cellular AMP : ATP ratio. AMPK is a major cellular regulator of lipid and glucose metabolism. The activated AMPK phosphorylates and inactivates HMG-CoA reductase (encoded by gene *HMGCR*), MTOR (target of rapamycin); ACC-2 (encoded by gene *ACACB*); ACC (encoded by gene *ACACA*), glycerol-3-phosphate acyltransferase (encoded by gene *GPAM*); and carbohydrate response element-binding protein. The activation of AMPK by metformin also suppresses the expression of SREBP-1 (encoded by gene *SREBF1*), a key lipogenic transcription factor. Phosphorylated AMPK also activates SiRT1 and increases Pgc-1a (encoded by gene *PPARGC1A*) expression in the nucleus, leading to the downstream activation of mitochondrial biogenesis.

Metformin disrupts the coactivation of PXR with SRC1, resulting in the downregulation of CYP3A4 gene expression. Finally, activated AMPK results in an increase in glucose uptake in skeletal muscle by increasing the GLUT4 (encoded by gene *SLC2A4*) translocation activity. The overall pharmacological effect of AMPK activation in the liver includes the stimulation of fatty acid oxidation with inhibition of cholesterol and triglyceride synthesis. Peripheral effects include the stimulation of fatty acid oxidation and glucose uptake in skeletal muscle as well as a systemic increase in insulin sensitivity. However, the role of Metformin in insulin-mediated glucose uptake has been debated.

Pharmacokinetics

Absorption:

The absolute bioavailability of a Metformin hydrochloride 500 mg tablet given under fasting conditions is approximately 50–60%. Studies using single oral doses of Metformin hydrochloride immediate-release tablets 500 mg to 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of Metformin, as shown by approximately a 40% lower

mean peak plasma concentration (C_{max}), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35-minute prolongation of time to peak plasma concentration (T_{max}) following administration of a single 850-mg tablet of Metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.
Low-fat and high-fat meals increased the systemic exposure (as measured by AUC) from 500 mg Metformin tablets by about 38% and 73%, respectively, relative to fasting. Both meals prolonged Metformin T_{max} by approximately 3 hours but C_{max} was not affected.

Distribution:

The apparent volume of distribution (V/F) of Metformin following single oral doses of Metformin hydrochloride tablets 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of Metformin hydrochloride tablets, steady state plasma concentrations of Metformin are reached within 24–48 hours and are generally <1 µg/mL. During controlled clinical trials of Metformin, maximum Metformin plasma levels did not exceed 5 µg/mL, even at maximum doses.

Metabolism:

Intravenous single-dose studies in normal subjects demonstrate that Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion

Excretion:

Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of Metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Pharmacokinetics in Elderly Patients:

Limited data from controlled pharmacokinetic studies of Metformin in healthy elderly subjects suggest that total plasma clearance of Metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in Metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

TENEPAN-M 500 AND TENEPAN-M 1000 STORAGE AND STABILITY

Store between 15°C and 30°C.

TENEPAN-M 500 AND TENEPAN-M 1000 SPECIAL HANDLING INSTRUCTIONS

No special instruction.

TENEPAN-M 500 & TENEPAN-M 1000 DOSAGE FORMS, COMPOSITION AND PACKAGING

Each tablet of TENEPAN-M 500 contains Teneligliptin 20 mg and Metformin 500 mg.

Each tablet of TENEPAN-M 1000 contains Teneligliptin 20 mg and Metformin 1000 mg.

Each strip of TENEPAN-M 500 and Tenepan-M 1000 contains 10 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance: Teneligliptin

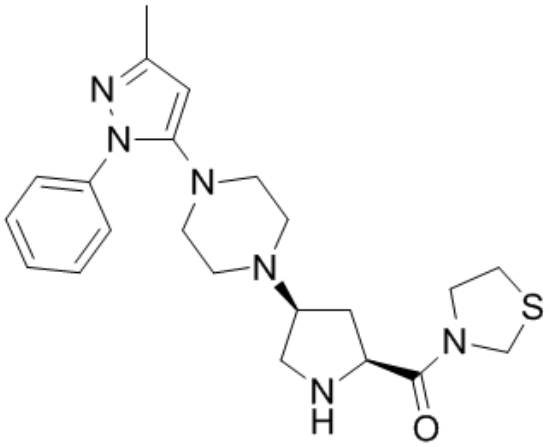
Proper Name: Teneligliptin Hydrobromide Hydrate.

Chemical Name: {(2S,4S)-4-[4-(3-Methyl-1-phenyl-1H-pyrazol-5-yl)-1-piperazinyl]-2-pyrrolidinyl}(1,3-thiazolidin-3-yl)methanone.

Molecular Formula: $C_{22}H_{30}N_6OS$**.** 2 ½ HBr **.** xH_2O

Molecular Mass: 628.86

Structural Formula:



HBr . xH_2O

Fig 1: Chemical Structure of Teneligliptin

Drug Substance: Metformin

Proper Name: Metformin hydrochloride

Chemical Name: N,N-Dimethylimidodicarbonimidic diamide

Molecular Formula: $C_4H_{11}N_5 \bullet HCl$

Molecular Mass: 165.63

Structural Formula:

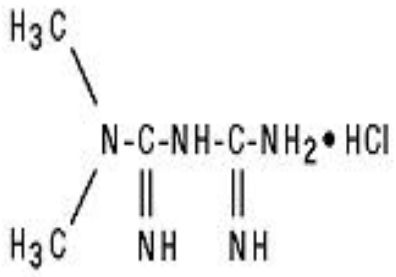


Fig 2: Chemical Structure of Metformin

CLINICAL TRIAL

Efficacy and safety of Teneligliptin, a dipeptidyl peptidase-4 inhibitor, combined with Metformin in Korean patients with type 2 diabetes mellitus

OBJECTIVE: The aim of the present study was to assess the efficacy and safety of Teneligliptin in combination with Metformin in type 2 diabetes mellitus who were inadequately controlled with Metformin monotherapy.

MATERIALS AND METHODS: In a phase III, randomized, double-blind, placebo controlled, parallel-group clinical trial of 16 weeks, patients with type 2 diabetes were eligible to participate if they had inadequate glycemic control [glycated haemoglobin (HbA1c) levels 7.0–10.0%] on stable-dose Metformin monotherapy (≥1000mg/day) for at least 8 weeks. Patients who had type 1 diabetes mellitus, current or a history of significant comorbidities, such as cardiovascular, hepatic and renal conditions, were excluded from the study. After the 2-week run-in period, eligible patients were assigned 2:1 to a 20 mg Teneligliptin once daily or a placebo once daily group, respectively. The Metformin dose was kept constant throughout the study period. A change from baseline in patients' HbA1c levels after 16 weeks of treatment was used as the primary efficacy endpoint. Safety and tolerability were assessed throughout the study. The changes from baseline to week 16 were compared between the two groups using analysis of covariance, with site as affixed effect t and baseline HbA1c level as a covariate.

RESULTS: The adjusted mean changes from baseline values were −0.90% for the Teneligliptin plus Metformin group compared with−0.12% for the placebo plus Metformin group ($p<0.0001$). A greater decrease in HbA1c was observed in the Teneligliptin plus Metformin group compared with the Placebo plus Metformin group at week 4 and throughout the randomized treatment period (Figure 3). The adjusted mean change in fasting plasma glucose from baseline to week 16 was −0.93 mmol/l (16.79mg/dl) for the Teneligliptin plus Metformin group versus +0.32 mmol/l (5.69mg/dl) for the Placebo plus Metformin group ($p<0.0001$). A significantly greater proportion of patients achieved a therapeutic glycemic response (HbA1c<7%) with Teneligliptin plus Metformin than with Placebo plus Metformin (64.71 vs. 13.24%, respectively; $p<0.001$). Greater increases in β-cell function based on homeostasis model assessment of β-cell function (HOMA-β) were observed in patients treated with Teneligliptin plus Metformin compared with those treated with placebo plus Metformin at week 16 ($p=0.0008$). Homeostasis model assessment of insulin resistance (HOMA-IR) showed an improving trend in patients treated with Teneligliptin plus Metformin compared with placebo plus metformin ($p=0.1754$). No differences were observed between treatment groups in the exploratory efficacy endpoints of body weight, fasting insulin, fasting C-peptide, high-sensitivity C-reactive protein or lipid variables.

CONCLUSION: The addition of Teneligliptin to Metformin treatment was effective and well tolerated in Korean patients with type 2 diabetes.

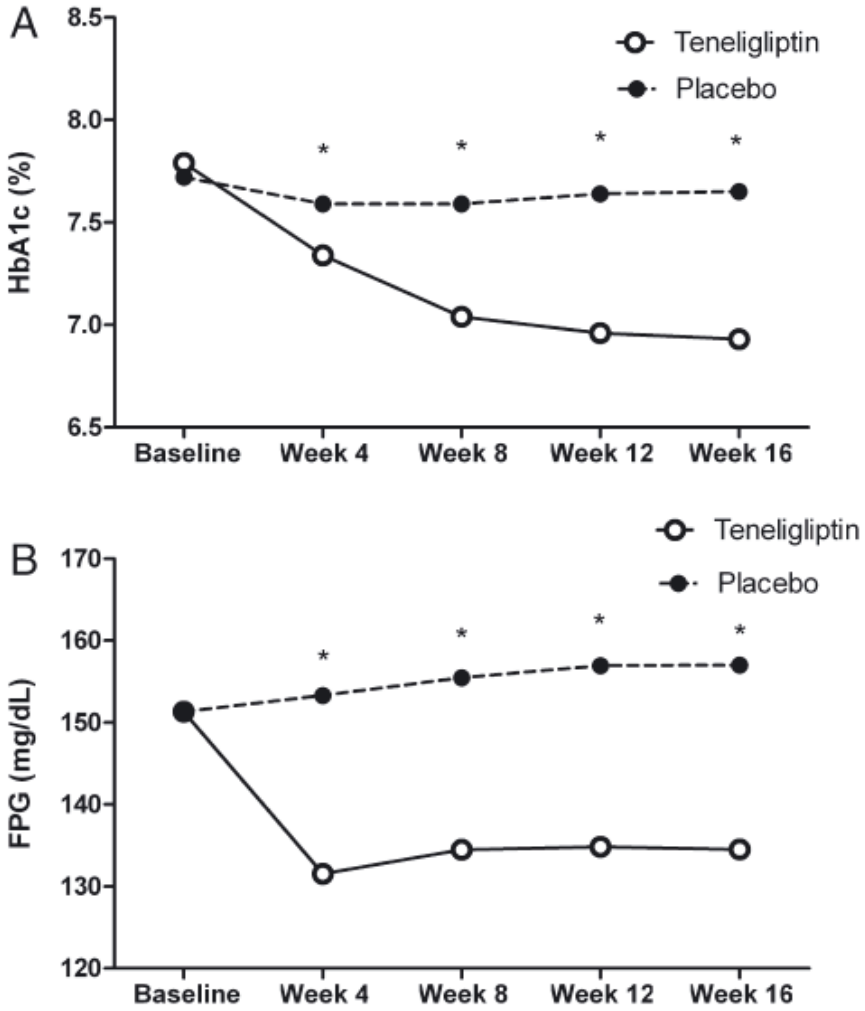


Figure 3: Glycemic control in patients treated with Teneligliptin plus Metformin or Placebo plus Metformin during the randomized treatment period: (A) Mean glycated haemoglobin (HbA1c) and (B) mean fasting plasma glucose (FPG) values during the randomized treatment period. (*p value<0.001. p values are for comparisons between the Teneligliptin and Placebo groups).

Toxicology

Teneligliptin:

Toxicology studies including single-dose toxicity, repeated-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, and other toxicity studies (antigenicity & immune-toxicity studies) have been conducted with Teneligliptin.

1. Single dose toxicity: Single dose oral toxicity studies have been performed in wistar rats and cynomolgus monkey upto dose of 2000 mg/kg.

2. Repeat dose toxicity: Repeated dose oral toxicity studies have been reported in wistar rats and cynomolgus monkey. In 2-, 13- & 26-weeks repeat dose toxicity study in rats, no observed adverse effect level (NOAEL) was 100, 30 and 10 mg/kg, respectively. While, in 4-, 13- and 52-weeks repeat dose toxicity study in monkeys, NOAEL was 60, 30 and 30 mg/kg, respectively. The accumulation ratio for $AUC_{0\text{-}24\ h}$ was 1.5 to 2.2 in rats and 0.6 to 1.6 in monkeys in repeated dose pharmacokinetics studies.

3. Reproductive and developmental toxicity: Fertility and early embryonic development to implantation with Teneligliptin was studied in male rats at doses 0, 30, 70 & 150 mg/kg and in female rats at doses 0, 30, 100 & 200 mg/kg. The NOAEL was 70 mg/kg and 100 mg/kg for general condition, reproductive function, and early embryogenesis in male and female animals, respectively. In embryo-fetal development, Teneligliptin was non-teratogenic and non-embryotoxic in rats at doses 0, 10, 30 & 100 mg/kg and rabbits at doses 0, 10, 30 & 60 mg/kg. The embryo-fetal NOAEL was 30 mg/kg in both rat and rabbits. In pre- and post-natal developmental toxicity study, Teneligliptin was studied at doses 0, 10, 30 & 100 mg/kg. The NOAEL was 30 mg/kg for both general condition and function of maternal animals and for F1 pups.

4. Genotoxicity: Teneligliptin and its metabolites were negative for genotoxicity in both *in-vitro* bacterial reverse mutation tests and *in-vivo* bone marrow micronucleus tests in rats.

5. Carcinogenicity: In 26-week study in CB6F1-Tg rasH2 mice and 104-week study in wistar rats, Teneligliptin did not produce any increase in neoplastic lesions was observed at the tested doses. The NOAEL was 600 mg/kg in mice and 75 mg/kg and 100 mg/kg in male and female rats, respectively.

6. Antigenicity: Teneligliptin did not cause active systemic anaphylactic reaction and passive cutaneous anaphylactic reaction in guinea pigs and in rats.

7. Other toxicity studies: Teneligliptin was non-immunotoxic *in-vitro*, in models like CD3-induced T lymphocyte proliferation test and a mixed lymphocyte culture test.

Metformin:

Toxicology studies including chronic toxicity, carcinogenicity, mutagenesis, reproductive and developmental toxicity have been conducted with Metformin.

1. Chronic Toxicity: In a 26-week oral toxicity study in rats, decrease in body weight gains were observed at 450 and 900 mg/kg/day, and changes in clinical laboratory parameters (decreased total leukocyte, lymphocyte and neutrophil count) and in some organ weights were noted at 900 mg/kg/day. The no-observed-adverse-effect level was 150 mg/kg/day (approximately 1.5 times the maximum recommended human daily dose based on body surface area comparisons).

In a 39-week oral toxicity study in dogs, treatment-related effects in food consumption were limited to females at 80 mg/kg/day. The no-observed-adverse-effect level was 80 mg/kg/day (approximately 2.6 times the maximum recommended human daily dose based on body surface area comparisons).

2. Reproduction: Fertility of male or female rats was unaffected by Metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

3. Development: Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 times the maximum recommended human daily dose based on body surface area comparisons. Determination of fetal concentrations demonstrated a partial placental barrier to Metformin.

4. Mutagenesis: There was no evidence of a mutagenic potential of Metformin in the following in vitro tests: Ames test (S. typhimurium), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the in vivo mouse micronucleus test were also negative

5. Carcinogenicity: Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately three times the maximum recommended human daily dose based on body surface area comparisons. No evidence of carcinogenicity with Metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with Metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

A carcinogenicity study was also conducted via dermal administration in Tg.AC transgenic mice at doses up to and including 2000 mg/kg/day. No evidence of carcinogenicity was observed in either male or female mice.

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PART III: ABRIDGED PRESCRIBING INFORMATION

TENEPAN-M 500 Tablets
(Teneligliptin 20 mg / Metformin Hydrochloride Extended-Release 500 mg)
&
TENEPAN-M 1000 Tablets
(Teneligliptin 20 mg / Metformin Hydrochloride Extended-Release 1000 mg)

Composition: Each **Tenepan-M 500** Tablet contains Teneligliptin 20 mg and Metformin Hydrochloride Extended-Release 500 mg. Each **Tenepan-M 1000** Tablet contains Teneligliptin 20 mg and Metformin Hydrochloride Extended-Release 1000 mg.

Indication: Tenepan-M 500 and **Tenepan-M 1000** is indicated in patients with T2DM whose diabetes is not adequately controlled on Metformin or Teneligliptin alone or who are already treated with the combination of Teneligliptin and Metformin, as separate tablets

Mechanism of Action: Teneligliptin inhibits dipeptidyl peptidase-4 (DPP-4) enzyme, which degrades the active incretins GLP-1 (Glucagon like peptide-1) and GIP (Glucose-dependent insulinotropic peptide). By preventing GLP-1 and GIP degradation, Teneligliptin is able to increase the secretion of insulin by *beta*-cells and suppress the release of glucagon by *alpha*-cells of the pancreas.
Metformin improves glucose tolerance in patients with T2DM, lowering both basal and postprandial plasma glucose. It further decreases hepatic glucose production, decrease intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

Dosage and Administration: Tenepan-M 500 & Tenepan-M 1000: 1) Patients inadequately controlled on either Teneligliptin or Metformin monotherapy. 2) Patients switching from combination therapy of Teneligliptin plus Metformin Extended Release as separate tablets. 3) Drug naïve patients with entry HbA1c ≥7.5 %. 4) In combination with other oral antidiabetic drug (OAD) (i.e. triple combination therapy) as an adjunct to diet and exercise in adult patients inadequately controlled with Metformin and other OAD. Do not exceed maximum recommended dose (Teneligliptin 40 mg / Metformin Extended-Release 2000 mg) once daily, and should be given with meals to reduce the GI side effects associated with Metformin. Tenepan-M 500 should not be used in patients with hepatic impairment and in severe renal impairment (eGFR <30 mL/min/1.73m^2) whereas, Tenepan-M 1000 should not be used in patients with hepatic impairment and moderate to severe renal impairment (eGFR <60 mL/min/1.73m^2).

Contraindications: History of hypersensitivity to Teneligliptin / Metformin or to any of its excipients. Patients having severe ketoacidosis, diabetic coma or pre-coma and Type 1 DM (since a prompt correction of hyperglycemia is required by transfusion of insulin, the administration of Teneligliptin is not suitable). In conditions such as severe infection, peri-operative, severe trauma and severe external injury (since Glycemic Control is desired by insulin injection), the administration of Teneligliptin / Metformin is not recommended.

Warnings and Precautions: For allergic or hypersensitive reaction, seek emergency medical attention. Possible symptoms such as difficulty in breathing, difficulty in swallowing, swelling, chest tightness, skin rashes, and hives might occur. In patients taking Metformin, lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis. Lactic acidosis is a medical emergency that must be treated. Warn patients against excessive alcohol intake due to high risk of lactic acidosis. The safety of Teneligliptin / Metformin in pregnant and nursing women is not known.

Drug Interaction: No clinically relevant pharmacokinetic interaction was observed when Teneligliptin was co-administered with Metformin. Patients might suffer from hypoglycemia if Teneligliptin is given along with other hypoglycemic agents or *beta*-blocking agents and Monoamine oxidase inhibitor. Use of Antiarrhythmic drug with Teneligliptin may cause QT prolongation. Metformin may cause an increased risk of lactic acidosis in acute alcohol intoxication.

Adverse Effect: Teneligliptin studies reported few adverse reactions such as hypoglycemia, intestinal obstruction, liver dysfunction and interstitial pneumonia. Metformin commonly causes GI related adverse effects e.g. diarrhea, nausea, vomiting, abdominal pain, constipation, distention abdomen, dyspepsia/heartburn, flatulence and taste disturbance.