For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

TENEPURE- M

1. Generic Name

Teneligliptin and Metformin Hydrochloride Extended Release Tablets

2. Qualitative and quantitative composition

TENEPURE- M 500

Each uncoated bilayer tablet contains

Teneligliptin Hydrobromide Hydrate

equivalent to Teneligliptin ……20 mg

Metformin Hydrochloride I.P..……..500 mg

(As Extended Release)

Excipients……q.s.

Colour: Ferric Oxide Yellow USP-NF (in Teneligliptin Layer)

The excipients used are Opadry Yellow 06B82444, Hydrogenated Castor Oil, L-Hydroxy Propyl Cellulose, Guar Gum, Methyl Paraben, Maize Starch, Carboxy Methylcellulose Sodium, Starch, Microcrystalline Cellulose, Polyox WSR 301, Ferric Oxide Yellow, Magnesium Stearate, Propyl Paraben, Hydroxy Propyl Cellulose, Hydroxy Propyl Methyl Cellulose and Colloidal Silicon Dioxide.

TENEPURE- M 1000

Each uncoated bilayer tablet contains

Teneligliptin Hydrobromide Hydrate

equivalent to Teneligliptin ……20 mg

Metformin Hydrochloride I.P..……..1000 mg

(As Extended Release)

Excipients……q.s.

Colour: Ferric Oxide Yellow USP-NF (in Teneligliptin Layer)

The excipients used are Opadry Yellow 06B82444, Hydrogenated Castor Oil, L-Hydroxy Propyl Cellulose, Guar Gum, Methyl Paraben, Maize Starch, Carboxy Methylcellulose Sodium, Starch, Microcrystalline Cellulose, Polyox WSR 301, Ferric Oxide Yellow, Magnesium Stearate, Propyl Paraben, Hydroxy Propyl Cellulose, Hydroxy Propyl Methyl Cellulose and Colloidal Silicon Dioxide.

3. Dosage form and strength

Dosage form: Uncoated Bilayered Tablets

Strength:

TENEPURE- M 500

Teneligliptin 20 mg and Metformin Hydrochloride 500 mg

TENEPURE- M 1000

Teneligliptin 20 mg and Metformin Hydrochloride 1000 mg

4. Clinical particulars

4.1 Therapeutic indication

TENEPURE- M is used as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both teneligliptin and metformin is appropriate.

4.2 Posology and method of administration

Posology

The daily recommended dose is as directed by the Physician.

Method of administration

TENEPURE- M tablets should be administered orally. Do not crush or chew the tablet before swallowing.

4.3 Contraindications

- Hypersensitivity to the drug or any of its components
- Severe ketosis, diabetic coma or pre-coma and also for immediate remedy in type 1 Diabetes (since a prompt correction of hyperglycaemias is required) with infusion and insulin
- Severe trauma before and after surgery and when the blood glucose level is controlled with insulin injection
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis).
- Diabetic pre-coma.
- Severe renal failure (GFR < 30 mL/min).
- Acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock.
- Disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) such as: decompensated heart failure, respiratory failure, recent myocardial infarction, shock.
- Hepatic insufficiency, acute alcohol intoxication, alcoholism.

4.4 Special warnings and precautions for use

Teneligliptin

Careful administration recommended in:

- Patient with severe hepatic dysfunction as there is no usage experience and safety has not been established.
- Patient with heart failure (NYHA class III~IV) as there is no usage experience and safety has not been established.
- Patient under sulfonyl urea medication or Insulin formulations risk of hypoglycemia may increase
- Hypoglycemia may occur in patients with:
    - Adrenal insufficiency

- Malnutrition, starved state, irregular dietary intake, insufficient dietary intake or hyposthenia
- Vigorous muscular movement
- Patient with excessive alcohol consumption

- Patient with history of abdominal surgery or intestinal obstruction (intestinal obstruction might occur).
- QT prolongation may occur in patients having arrhythmia such as severe bradycardia or having its history, patient having heart disease such as congestive heart failure and patient having hypokalaemia.
- Acute pancreatitis has been reported in studies and since acute pancreatitis is also reported with similar molecules, it should not be used in patients with history of acute pancreatitis. In case a patient develops acute pancreatitis the drug should be withdrawn and immediate physician consultation should be done.

Important Precautions:

- The points regarding hypoglycaemia and its coping strategy should be sufficiently explained to the patient when using Teneligliptin. 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 o insulin formulation, consider decreasing the dose of sulfonylurea or insulin formulation when given in combination with teneligliptin.
- Consider its use only to the patient diagnosed with Type 2 diabetes mellitus (T2DM). In addition to T2DM, pay attention to diseases having symptoms (such as renal glycosuria, thyroid dysfunction) similar to diabetes, such as abnormal glucose tolerance/positive urine sugar.
- Consider the application of Teneligliptin in patients who have not sufficiently responded to diet and exercise therapy, which is a basic treatment for diabetes.
- During administration of Teneligliptin, regularly check the blood sugar; check the effect of the drug. In case, the drug effect is insufficient even after taking this Teneligliptin for 3 months, then change to other treatment.
- During continuous administration, there are cases that do not need medication, cases where dose has to be reduced, and cases where there is no effect or inadequate response due to complications of patient's infestation and infections; and therefore, pay attention to dietary intake, blood sugar level, and presence of infections, as well as, always take care of selection of drugs, dosage, and whether to continue the drug.
- Since there is a possibility that adverse reactions, such as QT prolongation, might occur. It is desirable to avoid the medication in the patients having QT prolongation or it history (such as hereditary QT prolongation syndrome) or the patients having history of Torsade's de pointes.
- Since there is a risk of hypoglycemia, attention should be paid while administration of this drug to the patients who are engaged in car driving or working at heights.
- In regards to the co-administration of this drug and insulin formulation, the efficacy and the safety has not been studied.

- This drug and GLP-1 receptor agonist both have GLP-1 receptor mediated antihyperglycemic effect. No clinical trial results are available regarding concomitant use of both drugs; also, effectiveness and safety have not been confirmed.

Other Precautions

In reported clinical trials, QT prolongation has been reported when 160 mg of this Teneligliptin was administered once daily. (Approved dose of this Teneligliptin: The usual dosage is 20 mg of teneligliptin once daily and the maximum dose is 40 mg once daily). When a repeated oral dose of 40 mg or 160 mg teneligliptin once daily to the healthy adults for four days, the maximum mean value (and 90% confidence interval upper limit) of placebo-corrected QTcI (QTc corrected per individual) interval change was 3.97 at 3 hours after dosing completion in 40 mg group and 9.3 msec at 1.5 hours after dosing completion in 160 mg group.

In a reported 52-week repeated oral administration toxicity test using cynomolgus monkey, the cutaneous symptoms, such as superficial abrasion, scab, or ulcer, were observed on the tail, extremities, and auricles with the dose of 75mg/kg/ day. AUC_{0-24hr} in this case reached to around 45 times when 40 mg/day was administered to humans. Note that the same toxicity findings have not been reported in other animal species (rats, mice, and rabbits) and humans.

Metformin Hydrochloride

Lactic acidosis

Lactic acidosis, a very rare, but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.

In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended.

Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis (see sections 4.3 and 4.5).

Patients and/or care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7.35), increased plasma lactate levels (>5 mmol/L) and an increased anion gap and lactate/pyruvate ratio.

Renal function

GFR should be assessed before treatment initiation and regularly thereafter, see section 4.2. Metformin is contraindicated in patients with GFR<30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function, see section 4.3.

Cardiac function

Patients with heart failure are more at risk of hypoxia and renal insufficiency. In patients with stable chronic heart failure, metformin may be used with a regular monitoring of cardiac and renal function.

For patients with acute and unstable heart failure, metformin is contraindicated (see section 4.3).

Administration of iodinated contrast agents

Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Metformin should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable, see sections 4.2 and 4.5.

Surgery

Metformin must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.

Other precautions

All patients should continue their diet with a regular distribution of carbohydrate intake during the day. Overweight patients should continue their energy-restricted diet.

The usual laboratory tests for diabetes monitoring should be performed regularly.

Metformin alone does not cause hypoglycaemia, but caution is advised when it is used in combination with insulin or other oral antidiabetics (e.g. sulfonylureas or meglitinides).

4.5 Drugs interactions

Teneligliptin

Drug name and other details	**Clinical symptoms and treatment methods**	**Mechanism and Risk factors**
Medicines for diabetic disease: · Sulfonylurea · Fast-acting insulin secretagogue · α- glucosidase inhibitor · Biguanides drugs · Thiazolidine drug · GLP-1 analogue preparation · SGLT2 inhibitor insulin preparation	Since hypoglycemia might occur, these drugs should be administered while carefully monitoring 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 hypoglycaemia is observed, usually, cane sugar should be given and when co-administered with α-glucosidase inhibitor, glucose should be given.	Hypoglycemic action is Increased.

Drugs increasing hypoglycaemic action · β-blocking agents · Salicylic acid drugs · Monoamine oxidase inhibitor	Since the blood sugar may further decrease, these drugs should be administered while carefully observing the patient's condition in addition to blood sugar level.	Hypoglycemic action is increased.
Drugs decreasing hypoglycaemic action · Adrenaline · Adrenocortical hormone · Thyroid hormone	Since the blood sugar may Increase, these drugs should be administered while carefully observing the patient's condition in addition to blood sugar level.	Hypoglycemic action is decreased.
Drugs known to cause QT prolongation **<u>Class IA anti-arrhythmic drug</u>** · Quinidine Sulphate Hydrate · Procainamide Hydrochloride **<u>Class III antiarrhythmic drugs:</u>** · Amiodarone Hydrochloride · Sotalol Hydrochloride	QT prolongation might occur.	QT prolongation is seen with single administration of these drugs.

<u>Glimepiride combination:</u>

Reportedly, when a repeated dose of 1 mg glimepiride for four days and a single combined dose (2nd day of glimepiride administration) of 40 mg teneligliptin were administered to the healthy adults (16), the ratio (90% confidence interval) of Cmax of teneligliptin and AUC0-∞ 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% confidence interval) of Cmax of glimepiride and AUC0-∞ 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.

<u>Pioglitazone combination:</u>

Reportedly, when a repeated dose of 40 mg pioglitazone for eight days and a repeated combined dose (6th to 8th day of pioglitazone administration) of 850 mg teneligliptin were

administered to the healthy adults, the ratio (90% confidence interval) of Cmax of teneligliptin and AUC0-24hr geometric mean value was 0.907 (0.853 –0.965) and 1.042 (0.997 - 1.089) with respect to single-dose administration of teneligliptin alone.

Furthermore, when a repeated-dose of 40 mg teneligliptin for (6th to 8th day of pioglitazone administration) of 850 mg teneligliptin of 850 mg metformin were administered to the healthy adults, the ratio (90% confidence interval) of Cmax of pioglitazone and AUC0-∞ 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% confidence interval) of Cmax of active metabolites (M-III and M-IV) of pioglitazone and AUC0-12 hr geometric mean value was 1.057 (0.974 - 1.148) and 1.206 (1.143 - 1.278) with respect to reported dose administration of metformin only, and AUC0-12 hr of Metformin increased 20.9 % due to co administration.

Metformin combination:

Reportedly, when a repeated dose of 40 mg teneligliptin once daily for eight days and a repeated combined dose (6th to 8th day of teneligliptin administration) of 850 mg metformin twice daily were administered to the healthy adults, the ratio (90% confidence interval) of Cmax of teneligliptin and AUC0-24hr 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% confidence interval) of Cmax of metformin and AUC0-12hr 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 teneligliptin alone, and it increased to 37% and 49% due to co-administration of metformin only, and the AUC0-12hr of metformin increased 20.9% due to co-administration).

Ketoconazole combination:

Reportedly, when a repeated dose of 400 mg ketoconazole for six days and a single combined does (4^{th} day of ketoconazole administration) of 20 mg teneligliptin were administered to the healthy adults, the ratio (90% confidence interval) of C_{max} of teneligliptin and AUC0-$_{0\text{-}12\,hr}$ geometric minimum mean-square value was 1.37 (1.25 - 1.50) and 1.49 (1.39 - 1.60) with respect to single-dose administration of teneligliptin alone, and it increased to 37% and 49% due to co- administration.

Metformin Hydrochloride

Concomitant use not recommended

Alcohol

Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in case *Iodinated contrast agents*

Metformin must be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable, see sections 4.2 and 4.4.

Combinations requiring precautions for use

Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE

inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.

Medicinal products with intrinsic hyperglycaemic activity (e.g. glucocorticoids (systemic and local routes) and sympathomimetics).

More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, adjust the metformin dosage during therapy with the other drug and upon its discontinuation.

Organic cation transporters (OCT)

Metformin is a substrate of both transporters OCT1 and OCT 2.

Co-administration of metformin with

- Inhibitors of OCT 1 (such as verapamil) may reduce efficacy of metformin.
- Inducers of OCT 1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.
- Inhibitors of OCT 2 (such as cimetidine, dolutegravir, ranolazine, trimethoprime, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.
- Inhibitors of both OCT 1 and OCT 2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.

Caution is therefore advised, especially in patients with renal impairment, when these drugs are co-administered with metformin, as metformin plasma concentration may increase. If needed, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the efficacy of metformin.

4.6 Use in special populaions (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Teneligliptin

Pregnancy

Teneligliptin should be used in pregnant women or in women who may possibly be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment. The safety of this Teneligliptin in pregnant women has not been established. Furthermore, the transfer to embryo in animal studies (rats) has been reported in literature.

Breast-feeding

Breast-feeding must be discontinued during administration of this Teneligliptin in lactating women (transfer to milk in animal studies (rats) has been reported in literature.

Pediatric Use

The safety of this Teneligliptin in low birth weight baby, new-born baby, infant, or little child has not been established.

Geriatric Use

In general, elderly patients often have physiological hypo function; and therefore, teneligliptin should be administered carefully.

Renal impairment

As determined from the pharmacokinetic characteristics of teneligliptin, the extent of increase in the exposure level of teneligliptin in patients with renal impairment will not pose any significant safety risk. Thus no dose adjustment is proposed in renal impaired patients.

Hepatic impairment

As determined from the pharmacokinetic characteristics of teneligliptin, the extent of increase in the exposure level of teneligliptin in patients with mild to moderate hepatic impairment will not pose any significant safety risk. Thus no dose adjustment is proposed in mild to moderate hepatic impaired patients. As per reported data, there was no clinical experience in severe degree hepatic impairment.

Metformin Hydrochloride

Pregnancy

Uncontrolled diabetes during pregnancy (gestational or permanent) is associated with increased risk of congenital abnormalities and perinatal mortality.

A limited amount of data from the use of metformin in pregnant women does not indicate an increased risk of congenital abnormalities. Animal studies do not indicate harmful effects with respect to pregnancy, embryonic or foetal development, parturition or postnatal development (see section 5.3).

When the patient plans to become pregnant and during pregnancy, it is recommended that diabetes is not treated with metformin but insulin be used to maintain blood glucose levels as close to normal as possible, to reduce the risk of malformations of the foetus.

Breast-feeding

Metformin is excreted into human breast milk. No adverse effects were observed in breastfed newborns/infants. However, as only limited data are available, breast-feeding is not recommended during metformin treatment. A decision on whether to discontinue breast-feeding should be made, taking into account the benefit of breast-feeding and the potential risk to adverse effects on the child.

Fertility

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.

4.7 Effects on ability to drive and use machines

TENEPURE- M tablets have no direct influence on the ability to drive and use machines but may cause hypoglycaemia.

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

Teneligliptin

The most frequent individual adverse event was hypoglycemia, dizziness, headache,

constipation, diarrhoea and pyrexia. Most of the adverse events are mild in severity.

a) Hypoglycemia

b) Intestinal Obstruction (0.1%)

c) Liver dysfunction (unknown frequency)

d) Interstitial pneumonia (frequency unknown)

(1) Significant adverse reactions:

a) Hypoglycemia:

Hypoglycemia may occur when co-administered with other drugs for diabetes (in combination with glimepiride: 8.9%, in combination with pioglitazone: 1.5%, in combination with glinides: 3.8%, in combination with Biguanides: 1.1%, and in combination with α-glucosidase inhibitor: 1.3%). Particularly, a severe hypoglycemia is noted when co-administered with other DPP-4 inhibitors, sulfonylurea, and also the cases with loss of consciousness are reported; and therefore, consider decreasing the quantity of sulfonylurea when co-administered with sulfonylurea. Furthermore, hypoglycemia (1.1%) is also reported when not co-administered with other drugs for diabetes. In case hypoglycemia is observed, appropriate measures must be taken such as intake of carbohydrate containing food.

b) Intestinal Obstruction (0.1%):

Intestinal obstruction may occur; and therefore, the patient should be carefully monitored.

If any abnormal findings, such as severe constipation, abdominal swelling, continuous abdominal pain, and vomiting, are observed, administration should be discontinued and appropriate measures must be taken.

c) Liver dysfunction (unknown frequency):

Liver dysfunction occurs with increase in AST (SGOT), ALT (SGPT); and therefore, appropriate measures such as performing sufficient monitoring of these parameters should be taken. Discontinue teneligliptin if abnormalities are observed.

d) Interstitial pneumonia (frequency unknown):

Interstitial pneumonia may occur. If coughing, breathing difficulty, onset of fever, and abnormal chest sounds (crepitation) are noticed, the examinations such as chest X-ray, chest CT, and serum maker should be carried out. In case interstitial pneumonia is suspected, the appropriate measures like discontinuation of administration and administration of adrenocortical hormone should be taken.

Other Adverse reactions

Incidence/Types 0.1% ~ 1% < 0.1%

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

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 (GOT), increased ALT (GPT), and increased γ-GTP and rise in Al-P

Kidney and urinary system: Albuminuria, positive ketone body in urine

Skin: Eczema a, Wet rash, pruritus, allergic dermatitis

Others: Increased CK (CPK), increased serum potassium, fatigue, allergic, rhinitis, and increased serum uric acid

Metformin Hydrochloride

During treatment initiation, the most common adverse reactions are nausea, vomiting, diarrhoea, abdominal pain and loss of appetite which resolve spontaneously in most cases. To prevent them, it is recommended to take TENEPURE- M in 2 or 3 daily doses and to increase slowly the doses.

The following adverse reactions may occur under treatment with TENEPURE- M. Frequencies are defined as follows: very common: ≥1/10; common >1/100, <1/10; uncommon >1/1,000, <1/100; rare >1/10,000, <1/1,000; very rare <1/10,000.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Metabolism and nutrition disorders	
Very rare	Lactic acidosis
	Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia.
Nervous system disorders	
Common	Taste disturbance
Gastrointestinal disorders	
Very common	Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent them, it is recommended that metformin be taken in 2 or 3 daily doses during or after meals. A slow increase of the dose may also improve gastrointestinal tolerability.
Hepatobiliary disorders	
Very rare	Isolated reports of liver function tests abnormalities or hepatitis resolving upon metformin discontinuation
Skin and subcutaneous tissue disorders	
Very rare	Skin reactions such as erythema, pruritus, urticaria

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any

point of contact of Torrent Pharma available at:
https://torrentpharma.com/index.php/site/info/adverse_event_reporting.
By reporting side effects, you can help provide more information on the safety of this medicine.

4.9 Overdose

Teneligliptin

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.

Metformin Hydrochloride

Hypoglycaemia has not been seen with metformin hydrochloride doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose of metformin or concomitant risks may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis.

5 Pharmacological properties

5.1 Mechanism of Action

Teneligliptin

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

Metformin Hydrochloride

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via 3 mechanisms:

- reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis.
- in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilization.
- and delay of intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase.

Metformin increases the transport capacity of all types of membrane glucose transporters (GLUTs) known to date.

5.2 Pharmacodynamic properties

Teneligliptin

<u>DPP-4 inhibitory action and GLP-1 degradation inhibitory action</u>

- Teneligliptin inhibits concentration-dependent human plasma DPP-4 activity, and its IC50 value (95% confidence interval) was 1.75 (1.62 - 1.89) nmol/L (in vitro).

- Teneligliptin concentration-dependently suppressed the degradation of GLP-1 in rat plasma, with IC50 values and its 95% CI being 2.92 nM [2.21, 3.87] (in vitro).
- In the glucose tolerance test using Zucker Fatty rat, an obesity model showing insulin resistance and abnormal glucose tolerance, teneligliptin increased plasma active GLP-1 concentration and plasma insulin concentration by its single dose administration.
- In patients having type 2 diabetes mellitus, the administration of 20 mg teneligliptin once daily inhibited the plasma DPP4 activity and increased the plasma active GLP-1 concentration.

Glucose tolerance improvement action

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

In patients having type 2 diabetes mellitus, the administration of 20 mg teneligliptin once daily improved the blood sugar after breakfast, lunch, and dinner and the fasting blood sugar.

Metformin Hydrochloride

Pharmacotherapeutic group: Blood glucose lowering drugs, Biguanides

ATC code: A10BA02

In reported clinical studies, use of metformin was associated with either a stable body weight or modest weight loss.

In humans, independently of its action on glycaemia, metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin reduces total cholesterol, LDL cholesterol and triglyceride levels.

Clinical efficacy

The prospective randomised reported study (UKPDS) has established the long-term benefit of intensive blood glucose control in adult patients with type 2 diabetes.

Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

- a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/1000 patient-years) versus diet alone (43.3 events/1000 patient-years), p=0.0023, and versus the combined sulfonylurea and insulin monotherapy groups (40.1 events/1000 patient-years), p=0.0034;
- a significant reduction of the absolute risk of diabetes-related mortality: metformin 7.5 events/1000 patient-years, diet alone 12.7 events/1000 patient-years, p=0.017;
- a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/1000 patient-years versus diet alone 20.6 events/1000 patient-years (p=0.011), and versus the combined sulfonylurea and insulin monotherapy groups 18.9 events/1000 patient-years (p=0.021);
- a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/1000 patient-years, diet alone 18 events/1000 patient-years (p=0.01).

Benefit regarding clinical outcome has not been shown for metformin used as second-line therapy, in combination with a sulfonylurea.

In type 1 diabetes, the combination of metformin and insulin has been used in selected patients, but the clinical benefit of this combination has not been formally established.

5.3 Pharmacokinetic properties

Teneligliptin

Plasma concentration:

Single-dose administration:

In a reported study, the plasma concentration changes and the pharmacokinetic parameters of teneligliptin after a single oral dose of 20 mg and 40 mg of teneligliptin given empty stomach to the healthy adults are shown below.

Table 1: Pharmacokinetic parameters at the time of single - dose oral drug administration in healthy adults

Strength	C (ng/mL)	AUC (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

n=6, Mean Value ± SD

T_{max} = Central value (minimum value - maximum value)

Repeated dose administration:

In the reported study the pharmacokinetic parameters of teneligliptin after a repeated dose of 20 mg of teneligliptin once daily for seven days given 30 minutes before breakfast to the healthy adults are shown below. It was thought that the state of equilibrium will be attained within seven days

Table 2: Pharmacokinetic parameters at the time of repeated - dose oral drug administration in healthy adults

	C_{max} (ng/mL)	AUC_{0-24hr} (ng.hr/mL)	AUC_{0-inf} (ng.hr/mL)	tmax (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 (0.4-2.0)	30.2±6.9

n=7, Mean Value ± SD

Tmax = Central value (minimum value - maximum value)

Influence of meal to drug Absorption

Cmax decreased after a single dose of 20 mg of teneligliptin given post meal to the healthy adults as compared to empty stomach and tmax prolonged from 1.1 hr to 2.6 hr; however, no difference observed in AUC.

Table 3: Pharmacokinetic parameters at the time of fasting and after food intake in healthy adults

	Cmax (ng/mL)	AUC0-24hr (ng.hr/mL)	AUC0-inf (ng.hr/mL)	tmax (hr)	t1/2 (hr)
Empty Stomach	232.2 (236.2±43.77)	1855.5 (1861.1±148.1)	2090.3 (2094.6±138.5)	1.1±0.4	26.5 (27.8±9.3)
Post Meal	184.9 (187.5±33.55)	1806 (1814.6±183.3)	2044.0 (2056.1±230.9)	2.6±1.1	26.9 (28.3±9.5)

n=14, Geometric mean (Arithmetic mean value ± Standard Deviation)

Tmax = Arithmetic mean value ± Standard Deviation

Rate of protein binding:

The protein binding ratio was 77.6 to 82.2% when the [ng/mL) was added to the human plasma (*in vitro*).

Metabolism

Following a single oral administration of 20 mg [^{14}C] label teneligliptin to the healthy adults, the unaltered substance and the metabolites M1, M2, M3, M4, and M5 were observed in the blood plasma. Furthermore, the ratio of $AUC_{0-\infty}$ of teneligliptin, M1, M2, M3, M4, and M5 with respect to $AUC_{0-\infty}$ calculated from the plasma radioactive concentration up to 72 hours after administration was 71.1%, 14.7%, 1.3%, 1.3%, 0.3%, and 1.1%.

Mainly, CYP3A4 and Flavin-containing monooxygenases (FMO1 and FMO3) participate in the metabolism of teneligliptin. Furthermore, although teneligliptin showed a weak inhibitory action towards CYP2D6, CYP3A4, and FMO (IC50 value: 489.4, 197.5, and 467.2μmol/L), it did not show inhibitory action towards CYP1A2, CYP2A6, CYP2B6, 1) CYP2C8, CYP2C8/9, CYP2C19, and CYP2E1, and CY P1A2 and CYP3A4 were not introduced (in vitro).

Excretion

When a single oral dose of 20 mg and 40 mg teneligliptin was given to the healthy adults on empty stomach, about 21.0 to 22.1% of dose was excreted as unaltered substance in urine, and the renal clearance was 37 to 39 mL/hr/kg.

When a 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 feces 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 feces excretion rate of unaltered substance, M1, M3, M4, and M5was26.1%, 4.0%, 1.6%, 0.3%, and 1.3%, respectively.

Teneligliptin is a substrate of P-glycoprotein that inhibited the transportation of digoxin up to 42.5% through P-glycoprotein in the concentration of 99μmol/L. Furthermore, teneligliptin showed a weak inhibitory action towards the organic anion transporter OAT 3 appeared in kidney, (IC50 value: 99.2μmol/L); however, it did not show 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 Cmax andt1/2 of teneligliptin depending on the extent/degree of renal dysfunction. On the other hand, in the mild renal dysfunction patient (Ccr ≥50 to ≥80mL/min), moderate renal dysfunction patient (Ccr ≥30 to ≥50mL/min), and severe renal dysfunction patient (Ccr<30mL/min), the AUC0-∞ was found to be about 1.25 times, 1.68 times, and 1.49 times, respectively, as compared to the healthy adults, and AUC0-43hr 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 Cmax of teneligliptin was found to be about 1.25 times and 1.38 times and AUC0-∞ was about 1.46 times and 1.59 times, respectively, in mild 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.

There is no clinical experience in high degree hepatic dysfunction patient (total score more than 9 by Child-Pugh classification).

Pharmacokinetics in Elderly Patient

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 patents) on empty stomach, the ratio (90% confidence interval) of geometric minimum mean-square value of elderly patient with Cmax, $AUC_{0-\infty}$, 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 Hydrochloride

Absorption

After an oral dose of metformin hydrochloride tablet, maximum plasma concentration (C_{max}) is reached in approximately 2.5 hours (t_{max}). Absolute bioavailability of a 500 mg or 850 mg metformin hydrochloride tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear.

At the recommended metformin doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 microgram/ml. In controlled clinical trials, maximum metformin plasma levels (C_{max}) did not exceed 5 microgram/ml, even at maximum doses.

Food decreases the extent and slightly delays the absorption of metformin. Following oral administration of a 850 mg tablet, a 40% lower plasma peak concentration, a 25% decrease

in AUC (area under the curve) and a 35 minute prolongation of the time to peak plasma concentration were observed. The clinical relevance of these findings is unknown.

Distribution

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean volume of distribution (Vd) ranged between 63-276 l.

Metabolism

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination

Renal clearance of metformin is > 400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours.

When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

Characteristics in specific groups of patients

Renal impairment

The available data in subjects with moderate renal insufficiency are scarce and no reliable estimation of the systemic exposure to metformin in this subgroup as compared to subjects with normal renal function could be made. Therefore, the dose adaptation should be made upon clinical efficacy/tolerability considerations (see section 4.2).

Paediatric population

Single dose study: After single doses of metformin hydrochloride 500 mg paediatric patients have shown similar pharmacokinetic profile to that observed in healthy adults.

Multiple dose study: Data are restricted to one study. After repeated doses of 500 mg twice daily for 7 days in paediatric patients the peak plasma concentration (C_{max}) and systemic exposure (AUC0-t) were reduced by approximately 33% and 40%, respectively compared to diabetic adults who received repeated doses of 500 mg twice daily for 14 days. As the dose is individually titrated based on glycaemic control, this is of limited clinical relevance.

6 Nonclinical properties

6.1 Animal Toxicology or Pharmacology

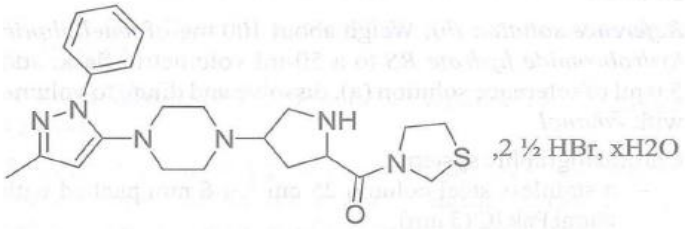
Metformin Hydrochloride

Preclinical data reveal no special hazard for humans based on conventional studies on safety, pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and reproductive toxicity.

7 Description

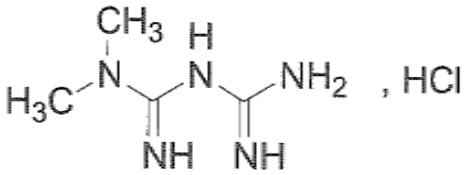
Teneligliptin

Teneligliptin Hydrobromide Hydrate is antidiabetic drug. The chemical name is {(2S, 4S)-4-[4-(3-methyl-1-phenyl-l*H*-pyrazol-5-yl) piperazine-1-yl]pyrrolidine-2-yl}(1,3-thiazolidine-3-yl)methanone hemipenta Hydrobromide hydrate having molecular weight of 628.9. Its empirical formula is ($C_{22}H_{30}N_6OS$, 2 ½ HBr, xH_2O with structural formula of



Metformin Hydrochloride

Metformin Hydrochloride is 1, 1-dimethylbiguanide hydrochloride. Having molecular formula $C_4H_{11}N_5HCL$ and molecular weight 165.6. The chemical structure is:



8 Pharmaceutical particulars

8.1 Incompatibilities

None Stated

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

TENEPURE- M 500 available in blister strips of 15 tablets.

TENEPURE- M 1000 available in blister strips of 10 tablets.

8.4 Storage and handing instructions

Store below 25°C, away from direct sunlight, heat and moisture.

Keep all medicines out of reach of children.

9 Patient Counselling Information

TENEPURE- M

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any questions, or if there is anything you do not understand, ask your doctor or pharmacist.

- **This medicine has been prescribed for you only.** Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1 What TENEPURE- M is and what it is used for

TENEPURE- M is a combination of two active ingredients Teneligliptin and Metformin. Teneligliptin which is an anti-diabetic drug belongs to the class DPP-4 inhibitors and Metformin Hydrochloride belongs to a group of medicines called biguanides.

TENEPURE- M is used as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both teneligliptin and metformin is appropriate.

9.2 What you need to know before you take TENEPURE- M

Do not take TENEPURE- M Tablets:

- If you are allergic to Teneligliptin or Metformin Hydrochloride or to any of the other ingredients of this medicine. An allergic reaction may cause a rash, itching or shortness of breath.
- If you have liver problems
- If you have severely reduced kidney function
- If you have uncontrolled diabetes, with, for example, severe hyperglycaemia (high blood glucose), nausea, vomiting, diarrhoea, rapid weight loss, lactic acidosis (see “Risk of lactic acidosis” below) or ketoacidosis. Ketoacidosis is a condition in which substances called 'ketone bodies' accumulate in the blood and which can lead to diabetic pre-coma. Symptoms include stomach pain, fast and deep breathing, sleepiness or your breath developing an unusual fruity smell
- If you lost too much water from your body (dehydration), such as due to long-lasting or severe diarrhoea, or if you have vomited several times in a row. Dehydration may lead to kidney problems, which can put you at risk for lactic acidosis (see 'Warnings and precautions').
- If you have a severe infection, such as an infection affecting your lung or bronchial system or your kidney. Severe infections may lead to kidney problems, which can put you at risk for lactic acidosis (see 'Warnings and precautions').

- If you are treated for acute heart failure or have recently had a heart attack, have severe problems with your circulation (such as shock) or have breathing difficulties. This may lead to a lack in oxygen supply to tissue which can put you at risk for lactic acidosis (see 'Warnings and precautions').
- If you are a heavy drinker of alcohol.
- If you are under 18 years of age.

Warnings and precautions

Risk of lactic acidosis

TENEPURE- M may cause a very rare, but very serious side effect called lactic acidosis, particularly if your kidneys are not working properly. The risk of developing lactic acidosis is also increased with uncontrolled diabetes, serious infections, prolonged fasting or alcohol intake, dehydration (see further information below), liver problems and any medical conditions in which a part of the body has a reduced supply of oxygen (such as acute severe heart disease).

If any of the above apply to you, talk to your doctor for further instructions.

Stop taking TENEPURE- M for a short time if you have a condition that may be associated with dehydration (significant loss of body fluids) such as severe vomiting, diarrhoea, fever, exposure to heat or if you drink less fluid than normal. Talk to your doctor for further instructions.

Stop taking TENEPURE- M and contact a doctor or the nearest hospital immediately if you experience some of the symptoms of lactic acidosis, as this condition may lead to coma.

Symptoms of lactic acidosis include:

- vomiting
- stomach ache (abdominal pain)
- muscle cramps
- a general feeling of not being well with severe tiredness
- difficulty in breathing
- reduced body temperature and heartbeat

Lactic acidosis is a medical emergency and must be treated in a hospital.

If you need to have major surgery you must stop taking TENEPURE- M during and for some time after the procedure. Your doctor will decide when you must stop and when to restart your treatment with TENEPURE- M.

If you are recovering from an injury, infections with fever, or from other forms of stress, inform your doctor as temporary change of treatment may be necessary

During treatment with TENEPURE- M, your doctor will check your kidney function at least once a year or more frequently if you are elderly and/or if you have worsening kidney function.

If you are older than 75 years, treatment with Glucophage SR should not be started to lower the risk of developing type 2 diabetes.

You may see some remains of the tablets in your stools. Do not worry- this is normal for this type of tablet.

You should continue to follow any dietary advice that your doctor has given you and you should make sure that you eat carbohydrates regularly throughout the day.

Do not stop taking this medicine without speaking to your doctor.

Other medicines and TENEPURE- M

If you need to have an injection of a contrast medium that contains iodine into your bloodstream, for example in the context of an X-ray or scan, you must stop taking TENEPURE- M before or at the time of injection. You may need more frequent blood glucose and kidney function tests, or your doctor may need to adjust the dosage of TENEPURE- M.

Tell your doctor if you are taking, have recently taken or might take any other medicines. You may need more frequent blood glucose and kidney function tests, or your doctor may need to adjust the dosage of Glucophage SR. It is especially important to mention the following:

- Medicines which increase urine production (diuretics (water tablets) such as furosemide).
- Medicines used to treat pain and inflammation (NSAID and COX-2 inhibitors, such as ibuprofen and celecoxib)
- Certain medicines for the treatment of high blood pressure (ACE inhibitors and angiotensin II receptor antagonists)
- Steroids such as prednisolone, mometasone, beclometasone.
- Sympathomimetic medicines including epinephrine and dopamine used to treat heart attacks and low blood pressure. Epinephrine is also included in some dental anaesthetics.
- Medicines that may change the amount of Glucophage SR in your blood, especially if you have reduced kidney function (such as verapamil, rifampicin, cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole, crizotinib, olaparib).

TENEPURE- M with alcohol

Avoid excessive alcohol intake while taking TENEPURE- M since this may increase the risk of lactic acidosis (see section ‘Warnings and precautions’).

Pregnancy, breast-feeding and fertility:

Pregnancy

TENEPURE- M Tablets should not be taken during pregancy. Tell your doctor if you are, you think you might be or are planning to become pregnant.

Breast feeding

TENEPURE- M may pass into breast milk. TENEPURE- M should not be taken during breast feeeding. Ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

TENEPURE- M on its own does not cause hypoglycaemia (a blood glucose level which is too low). This means that it will not affect your ability to drive or use machines. However, take special care if you take TENEPURE- M together with other medicines to treat diabetes

that can cause hypoglycaemia (such as sulphonylureas, insulin, meglitinides). Symptoms of hypoglycaemia include weakness, dizziness, increased sweating, fast heartbeat, vision disorders or difficulty in concentration. Do not drive or use machines if you start to feel these symptoms

9.3 How to take TENEPURE- M

Always take this medicine exactly as described in this leaflet or as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure taking this medicine

- Take this medicine by mouth just before or with the first main meal of the day (usually breakfast). If you do not have breakfast you should take the product on schedule as prescribed by your doctor. It is important not to leave out any meal when you are on TENEPURE- M Tablets
- Swallow the tablets whole with at least half glass of water. Do not crush or chew the tablets

If you take more TENEPURE- M than you should

If you have taken more TENEPURE- M than you should have, you may experience lactic acidosis. Symptoms of lactic acidosis are non-specific such as vomiting, bellyache (abdominal pain) with muscle cramps, a general feeling of not being well with severe tiredness, and difficulty in breathing. Further symptoms are reduced body temperature and heartbeat.

If you experience some of these symptoms, you should seek immediately medical attention, as lactic acidosis may lead to coma. Stop taking TENEPURE- M immediately and contact a doctor or the nearest hospital straight away.

If you forget to take TENEPURE- M Tablets

If you forget to take a dose, do not take a double dose to make up for forgotten doses.

If you stop taking TENEPURE- M Tablets

If you interrupt or stop the treatment you should be aware that the desired blood sugar lowering effect is not achieved or that the disease will get worse again. Keep taking TENEPURE- M Tablets until your doctor tells you to stop.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist or nurse.

9.4 Possible side effects

Like all medicines, TENEPURE- M can cause side effects, although not everybody gets them. The following side effects may occur: TENEPURE- M may cause a very rare (may affect up to 1 user in 10,000), but very serious side effect called lactic acidosis (see section ‘Warnings and precautions’). as lactic acidosis may lead to coma

Tell your doctor immediately if you experience any of the following symptoms :

Allergic reactions (including inflammation of blood vessels, often with skin rash) which may develop into serious reactions with difficulty in breathing, fall in blood pressure and sometimes progressing to shock

- Abnormal liver function including yellowing of the skin and eyes (jaundice), problems with the bile flow (cholestasis), inflammation of the liver (hepatitis) or liver failure

- Allergy (hypersensitivity) of the skin such as itching, rash, hives and increased sensitivity to sun. Some mild allergic reactions may develop into serious reactions
- Severe hypoglycaemia including loss of consciousness, seizures or coma.

Very common side effects (in more than 1 in 10 people)

digestive problems, such as feeling sick (nausea), being sick (vomiting), diarrhoea, bellyache (abdominal pain) and loss of appetite.

These side effects most often happen at the beginning of the treatment with TENEPURE-M. It helps if you spread the doses over the day and if you take TENEPURE- M with or straight after a meal. If symptoms continue, stop taking TENEPURE- M and talk to your doctor

Common side effects (in less than 1 in 10 people)

- changes in taste.

Rare side effects (may affect up to 1 in 1000 people)

- Lower blood sugar than normal (hypoglycaemia) (See Section 2)
- Decrease in the number of blood cells:
  - Blood platelets (which increases risk of bleeding or bruising)
  - White blood cells (which makes infections more likely)
  - Red blood cells (which can make the skin pale and cause weakness or breathlessness)

These problems generally get better after you stop taking TENEPURE- M tablets

Very rare side effects (may affect up to 1 in 10,000 people):

- Allergic reactions (including inflammation of blood vessels, often with skin rash) which may develop into serious reactions with difficulty in breathing, fall in blood pressure and sometimes progressing to shock. If you experience any of these symptoms, tell your doctor immediately.
- Abnormal liver function including yellowing of the skin and eyes (jaundice), impairment of the bile flow (cholestasis), inflammation of the liver (hepatitis) or liver failure. If you experience any of these symptoms , tell your doctor immediately.
- Feeling or being sick, diarrhoea, feeling full or bloated, and abdominal pain
- Decrease in the amount of sodium level in your blood (shown by blood tests)
- Lactic acidosis. This is a very rare but serious complication particularly if your kidneys are not working properly. Symptoms of lactic acidosis are non-specific (see section ‘Warning and precautions’)
- abnormalities in liver function tests or hepatitis (inflammation of the liver; this may cause tiredness, loss of appetite, weight loss, with or without yellowing of the skin or whites of the eyes). If this happens to you, stop taking TENEPURE- M and talk to your doctor.
- skin reactions such as redness of the skin (erythema), itching or an itchy rash (hives).
- low vitamin B12 levels in the blood.

Not known (frequency cannot be estimated from the available data)

- Allergy (hypersensitivity) of the skin may occur such as itching, rash, hives and increased sensitivity to sun. Some mild allergic reactions may develop into serious reactions with swallowing or breathing problems, swelling of your lips, throat or tongue. Therefore in the event of one of these side effects, tell your doctor immediately.
- Allergic reactions with sulfonylureas, sulfonamides, or related drugs may occur
- Problems with your sight may occur when beginning treatment with TENEPURE- M Tablets. This is due to changes in blood sugar levels and should soon improve
- Increased liver enzymes
- Severe unusual bleeding or bruising under the skin

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:
https://torrentpharma.com/index.php/site/info/adverse_event_reporting.
By reporting side effects, you can help provide more information on the safety of this medicine

9.5 How to store TENEPURE- M

Store below 25°C, away from direct sunlight, heat and moisture.

Keep all medicines out of reach of children.

9.6 Contents of the pack and other information

What **TENEPURE- M** contains

The active substances **TENEPURE- M** contains Teneligliptin and Metformin Hydrochloride.

TENEPURE- M 500

Teneligliptin 20 mg and Metformin Hydrochloride 500 mg

TENEPURE- M 1000

Teneligliptin 20 mg and Metformin Hydrochloride 1000 mg

The excipients used are Opadry Yellow 06B82444, Hydrogenated Castor Oil, L-Hydroxy Propyl Cellulose, Guar Gum, Methyl Paraben, Maize Starch, Carboxy Methylcellulose Sodium, Starch, Microcrystalline Cellulose, Polyox WSR 301, Ferric Oxide Yellow, Magnesium Stearate, Propyl Paraben, Hydroxy Propyl Cellulose, Hydroxy Propyl Methyl Cellulose and Colloidal Silicon Dioxide.

TENEPURE- M 500 available in blister strips of 15 tablets.

TENEPURE- M 1000 available in blister strips of 10 tablets

10 Details of manufacturer

Manufactured in India by :
Glenmark Pharmaceuticals Ltd,
B/2, Mahalaxmi Chambers, 22, Bhulabhai Desai Road, Mumbai 400 026.
At : Plot No. 21-22, Pharmacity, Selaqui, Distt. Dehradun - 248 011, Uttarakhand

11 Details of permission or licence number with date

Mfg Lic No. 1/UA/LL/2018 issued on 04.06.2020

12 **Date of revision**

Not Applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/TENEPURE- M 20, 500/1000mg/APR-21/01/PI