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

Not to be sold by retail without the prescription of a Registered Medical Practitioner

Prescribing Information

1. Generic Name

Teneligliptin 20 mg and Metformin Hydrochloride 500 mg (Sustained Release) Tablets
(Brand Name: TENEBLU®-M Tablets Tablets)

Teneligliptin 20 mg and Metformin Hydrochloride 1000 mg (Sustained Release) Tablets
(Brand Name: TENEBLU®-M Forte Tablets)

2. Qualitative and Quantitative Composition

TENEBLU-M Tablets
Each uncoated bilayered tablet contains:
Teneligliptin Hydrobromide Hydrate equivalent to Teneligliptin ……..… 20 mg.
Metformin Hydrochloride IP (in sustained release form) ……..…… 500 mg.
Excipients ……... q.s.
Colours: Ferric Oxide Yellow USP-NF (In Teneligliptin Layer).

TENEBLU-M Forte Tablets
Each uncoated bilayered tablet contains:
Teneligliptin Hydrobromide Hydrate equivalent to Teneligliptin …… 20 mg.
Metformin Hydrochloride IP (in sustained release form) ……..… 1000 mg.
Excipients ……..… q.s.
Colours: Ferric Oxide Yellow USP-NF (In Teneligliptin Layer).

3. Dosage Form and Strength

Dosage Form: Tablets.
Dosage Strength: Teneligliptin 20 mg with metformin hydrochloride (in sustained release form) 500 mg per tablet and teneligliptin 20 mg with metformin hydrochloride (in sustained release form) 1000 mg per tablet.

4. Clinical Particulars

4.1 Therapeutic Indication

TENEBLU-M and TENEBLU-M Forte Tablets are indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with either metformin or teneligliptin monotherapy is not adequate.

TENEBLU-M Forte Tablets are also indicated when glycaemic control is not achieved with 1000 mg of metformin monotherapy, especially in obese type 2 diabetic patients

TENEBLU-M and TENEBLU-M Forte Tablets controls hyperglycemia and thus, prevents or delays microvascular and macrovascular complications associated with it.

4.2Posology and Method of Administration

TENEBLU-M Tablets: Usual recommended dose in adults with type 2 diabetes is 1 tablet orally once daily. Based on response to initial therapy, dosage can be increased after a 2 to 4 week interval. Adjust the dosing based on effectiveness and tolerability, while not exceeding the maximum recommended daily dose of 40 mg teneligliptin and 2000 mg of metformin hydrochloride.

TENEBLU-M Forte Tablets: Usual recommended dose in adults is 1 tablet orally once daily, preferably in overweight or obese type 2 diabetic patients. If glycemic control is optimum, continue the dose as maintenance therapy. If effect is not satisfactory, consider a change to more appropriate treatment.

TENEBLU-M and TENEBLU-M Forte Tablets can be administered with or without a meal. However, taking tablets with or just after food may reduce gastrointestinal symptoms associated with metformin. Swallow tablet whole with water and strictly not to cut, crush or chew.

Or, as prescribed by the Physician.

4.3Contraindications

TENEBLU-M Tablets and TENEBLU-M Forte Tablets are contraindicated in the following:

- Known hypersensitivity to teneligliptin or to metformin or to any components of the formulation.
- Type 1 diabetic patient.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.
- Patients with severe infection, surgery, severe trauma (it is advised to control blood glucose level by insulin).
- Acute or chronic disease which may cause tissue hypoxia such as cardiac or respiratory failure, recent myocardial infarction, shock.
- Hepatic insufficiency, acute alcohol intoxication, alcoholism (due to the metformin component).
- Severe renal impairment (eGFR below 30 ml/min/1.73 m^2).

4.4Special Warnings and Precautions for Use

Teneligliptin

General: Teneligliptin is not a substitute for insulin in insulin-requiring patients. Teneligliptin should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Hypoglycaemia: Sulphonylureas such as gliclazide, glipizide, or glimepiride are known to cause hypoglycaemia. Patients receiving teneligliptin in combination with a sulphonylurea may be at risk for hypoglycaemia. Therefore, a lower dose of sulphonylurea may be considered to reduce the risk of hypoglycaemia.

Hypoglycemia may also occur in patients with adrenal insufficiency, malnutrition, starved state, irregular dietary intake, insufficient dietary intake or hyposthenia, vigorous muscular movement, or in patient with excessive alcohol consumption.

Pancreatitis: Acute pancreatitis has been observed in post marketing studies. Further, acute pancreatitis is also reported with similar molecules such as vildagliptin. Thus, teneligliptin should not be used in patients with history of acute pancreatitis. In case a patient develops acute pancreatitis, teneligliptin should be immediately discontinued and consult treating physician.

Hepatic Impairment: Teneligliptin should be administered with caution in patient with severe hepatic dysfunction as safety has not been established in these patients.

Heart Failure: Teneligliptin should be administered with caution in patient with heart failure (NYHA class III-IV) as there is no usage experience and safety has not been established.

Abdominal Surgery: Use teneligliptin with caution in patient with history of abdominal surgery or intestinal obstruction as there is risk of intestinal obstruction.

QT Prolongation: 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 hypokalemia.

Arthralgia: There have been post marketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

Metformin

Lactic Acidosis: Lactic acidosis is a rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by assessing other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency, and any condition associated with hypoxia. If metformin-associated lactic acidosis is suspected, immediately discontinue metformin therapy and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.

The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients.

Excessive Alcohol Intake: Alcohol is known to potentiate the effect of metformin on lactate metabolism. Acute alcohol intoxication is associated with an increased risk of lactic acidosis. Warn patients against excessive alcohol intake while receiving metformin therapy.

Radiologic Studies with Iodinated Contrast Media: Intravascular administration of iodinated contrast media may lead to renal failure, resulting in metformin accumulation and a risk of lactic acidosis. Metformin hydrochloride must be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Hypoxic States: Cardiovascular collapse (shock) of any kind, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on metformin therapy, the drug should be promptly discontinued.

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.

Renal Function: As metformin is excreted by the kidney, creatinine clearance should be determined before initiating treatment and regularly thereafter at least annually in patients with normal renal function and at least 2 to 4 times a year in patients with creatinine clearance levels at the upper limit of normal and in elderly subjects.

Loss of Blood Glucose Control: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold oral antidiabetic agents and temporarily administer insulin. Metformin may be reinstituted after the acute episode is resolved.

Surgery: Metformin should be discontinued 48 hours before elective surgery with general spinal or peridural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or when normal renal function has been established.

Hepatic Impairment: Patients with hepatic impairment have developed cases of metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of metformin in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B12 Deficiency: Long-term use of metformin may decrease absorption of vitamin B12 with resultant decrease in plasma B12 levels. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, may be associated with anemia, but appears to be rapidly reversible with discontinuation of metformin or vitamin B12 supplementation. Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. It is recommended to measure

hematologic parameters on an annual basis and vitamin B12 at 2 to 3 year intervals in patients on metformin therapy.

Other Precautions: 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 antidiabetic drugs.

4.5Drug Interactions

Teneligliptin

Ketoconazole: Teneligliptin is metabolized by CYP3A4 and is a weak substrate of P-glycoprotein. Ketoconazole is an inhibitor of CYP3A4 and P-glycoprotein. Exposure to teneligliptin, when administered in combination with ketoconazole, was less than twice the exposure to teneligliptin alone, which suggests that drugs that inhibit CYP3A4 (such as ketoconazole) are unlikely to increase the teneligliptin concentration in the plasma. Thus, teneligliptin can be administered with ketoconazole.

Antidiabetic Drugs: No clinically relevant drug-drug interactions were observed when teneligliptin was co-administered with metformin, canagliflozin, glimepiride, or pioglitazone in healthy volunteers; therefore, no dose adjustment of teneligliptin is required when it is co-administered with these drugs. Furthermore, teneligliptin did not affect the pharmacokinetic properties of metformin, canagliflozin, glimepiride, or pioglitazone.

Drugs Affecting Glycemic Control: Teneligliptin should be used with caution with drugs that can enhance the blood glucose lowering effects (e.g., β-blockers, MAO inhibitors, etc.) or attenuate the blood glucose lowering effects (like steroids, thyroid hormones, etc.).

Metformin

Carbonic Anhydrase Inhibitors (e.g., topiramate, zonisamide, acetazolamide or dichlorphenamide): Carbonic anhydrase inhibitors frequently cause a decrease in serum bicarbonate and induce hyperchloremic non-anion gap metabolic acidosis. Concomitant use of these drugs with metformin may increase the risk for lactic acidosis. More frequent monitoring of these patients is recommended.

Drugs that Reduce Metformin Clearance (e.g., ranolazine, vandetanib, dolutegravir, and cimetidine): Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors) could increase systemic exposure to metformin and may increase the risk for lactic acidosis.

Drugs Affecting Glycemic Control (e.g., thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid): These drugs tend to produce hyperglycemia and may lead to loss of glycemic control. When these drugs are administered to a patient receiving metformin, observe the patient closely for loss of blood glucose control. When

such drugs are withdrawn from a patient receiving metformin, observe the patient closely for hypoglycemia.

Insulin Secretagogues or Insulin: Co-administration of metformin with an insulin secretagogue (e.g., sulfonylurea) or insulin may increase the risk of hypoglycemia. Patients receiving an insulin secretagogue or insulin may require lower doses of the insulin secretagogue or insulin.

Combinations Requiring Precautions for Use:

1. Some drugs may adversely affect renal function which may increase the risk of lactic acidosis, e.g., NSAIDs, including selective cyclooxygenase (COX)-2 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.
2. Glucocorticoids (systemic and local routes), beta 2-agonists, and diuretics have intrinsic hyperglycemic activity. More frequent blood glucose monitoring, especially at the beginning of treatment is required. If necessary, adjust the metformin dosage during therapy with these drugs and upon its discontinuation.
3. ACE-inhibitors may decrease the blood glucose levels. If necessary, adjust the metformin dosage during therapy with these drugs and upon its discontinuation.

4.6Use in Special Populations

Pregnant Women

There are no adequate data available for use of teneligliptin and metformin combination therapy in pregnant women. The potential risk for humans is unknown. Therefore, this product should be used during pregnancy only if clearly needed and if the potential benefit justifies the possible risk to the fetus.

Lactating Women

It is unknown whether teneligliptin is excreted in human milk but, metformin excretes in human milk in low amounts. Animal studies (rat) have shown excretion of both teneligliptin and metformin in milk. Due to potential risk of neonate hypoglycaemia related to metformin, TENEBLU-M Tablets and TENEBLU-M Forte Tablets are not recommended for use during breast-feeding. If drug therapy is necessary, breast-feeding should be discontinued during administration of this product in lactating women.

Paediatric Patients

Safety and efficacy of teneligliptin with metformin combination therapy has not been established in children and adolescents. Thus, TENEBLU-M Tablets and TENEBLU-M Forte Tablets are not recommended for use in paediatric patients.

Geriatric Patients

Dose adjustments are usually not necessary for elderly patients. As metformin is excreted via the kidney and elderly patients have a tendency to decreased renal function (physiological hypofunction), use this product with caution in them and monitor their renal function regularly.

Renal Impairment Patients

Although, teneligliptin can be used in diabetes patients with renal impairment, metformin should be used with caution as it is eliminated by kidney. In patients with impaired renal function, usually lower dosage should be administered. A glomerular filtration rate (GFR) should be assessed before initiation of treatment with metformin-containing products and at least annually thereafter. If GFR is >60 ml/min, usually dosage adjustment is not required. Metformin-containing preparations are contraindicated in patients with GFR < 30 ml/min.

Hepatic Impairment Patients

Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. TENEBLU-M Tablets and TENEBLU-M Forte Tablets should not be used in patients with hepatic impairment.

In patients with severe renal or hepatic impairment, insulin is usually administered to control blood glucose level.

4.7Effect on Ability to Drive and Use Machines

Data is not available on the effects of teneligliptin with metformin combination therapy on ability to drive and use machines. Patients who experience dizziness as an adverse reaction should avoid driving vehicles or using machines. Further, patients should be cautioned about the risk of hypoglycaemia especially when this medicine is co-administered with sulphonylurea and/or insulin.

4.8Undesirable Effects

Teneligliptin

The most common adverse reactions reported with teneligliptin are hypoglycemia and constipation. Other adverse reactions reported with the use of teneligliptin may include:

- General: Fatigue, headache, dizziness, pyrexia.
- Gastrointestinal Disorders: Intestinal obstruction, abdominal bloating, abdominal discomfort, nausea, vomiting, abdominal pain, flatulence, stomatitis, gastric polyps, colon polyps, duodenal ulcer, reflux esophagitis, diarrhea, loss of appetite, acute pancreatitis.
- Liver: Increased AST (SGOT), increased A L T (SGPT), and increased γ -GTP
- Kidney and Urinary System: Proteinuria, positive ketone bodies in urine.
- Skin and Subcutaneous Tissue Disorders: Eczema, rash, itching, allergic dermatitis.
- Respiratory System: Allergic rhinitis, nasopharyngitis, pneumonia.
- Laboratory Investigations: Increase in serum levels of one or more of the following- amylase, lipase, CPK, potassium, uric acid.

Metformin

The most common adverse reactions reported with metformin are nausea, vomiting, diarrhoea, indigestion, abdominal pain, abdominal discomfort, constipation, dyspepsia/heartburn, flatulence, dizziness, taste disturbance, headache, upper respiratory infection, asthenia, and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. Very rarely metformin may cause skin reactions such as erythema, pruritus, urticaria; abnormal liver function test or hepatitis; and lactic acidosis which generally resolve upon metformin discontinuation.

Cholestatic, hepatocellular, and mixed hepatocellular liver injury have been reported with post-marketing use of metformin.

4.9 Overdose

Teneligliptin

No overdose toxicity has been reported with teneligliptin. In the event of an overdose, the usual supportive measures can be initiated, e.g., remove unabsorbed drug from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and if required, institute supportive therapy.

Metformin

Overdose of metformin hydrochloride has been reported with ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases. Lactic acidosis is a medical emergency and must be treated in hospital. Metformin is dialyzable, with a clearance of up to 170 ml/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of the accumulated drug from patients in whom metformin overdose is suspected.

5. Pharmacological Properties

5.1 Mechanism of Action

Teneligliptin

Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. These hormones are rapidly inactivated by the enzyme, dipeptidyl peptidase-4 (DPP-4). The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular signaling pathways involving cyclic AMP. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production.

Teneligliptin acts as a competitive reversible inhibitor of DPP-4 and decreases the degradation of incretins, especially GLP-1, thereby improving hyperglycemia by stimulating insulin secretion and suppressing glucagon secretion in a glucose-dependent manner (no or negligible risk of hypoglycemia).
Teneligliptin is a potent, selective, and long-lasting DPP-4 inhibitor that has approximately 700- to 1500-fold greater affinity for DPP-4 than other DPP enzymes, such as DPP-8 and DPP-9. Teneligliptin inhibits recombinant human DPP-4 and human plasma DPP-4 in a concentration-dependent manner: concentrations producing half maximal inhibition (IC_{50}) are 0.889 nmol/l and 1.75 nmol/l, respectively.
Teneligliptin binds with the S2 extensive subsite of DPP-4 via strong hydrophobic interactions mediated by an 'anchor lock domain'. These interactions may be related to the stronger potency of DPP-4 inhibition and longer duration of action of teneligliptin.

Metformin

Metformin is a biguanide class of oral antidiabetic drugs. Metformin produces its antihyperglycemic effects via following 3 mechanisms:

1. Reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis.
2. In muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation.
3. Delay of intestinal glucose absorption.

5.2Pharmacodynamic Properties

Teneligliptin

Teneligliptin is a selective and long-acting inhibitor of DPP-4 enzyme. By DPP-4 inhibition, teneligliptin prevented the degradation of incretins (GLP-1 and GIP) and promote insulin release. By increasing incretin hormone levels, teneligliptin increases insulin secretion and thereby decreases fasting and postprandial plasma glucose levels. Teneligliptin may also reduce plasma triglyceride levels through a sustained increase in GLP-1 levels. Teneligliptin has antioxidative properties and has shown endothelial protective effects in several non-clinical and clinical studies.

Metformin

Metformin is a biguanide with antihyperglycemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.
Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of all types of membrane glucose transporters (GLUT). In clinical studies, the major non-glycemic effect of metformin is either weight neutral or modest weight loss.

5.3Pharmacokinetic Properties

Teneligliptin

Absorption: Teneligliptin shows dose-dependent increases in the maximal plasma concentration (Cmax) and area under the plasma concentration-time curve (AUC). Peak plasma concentration i.e., Cmax of teneligliptin 20 mg is 187.20 ng/ml and its Tmax is 1.8 hours. After repeated doses of teneligliptin 20 or 80 mg, no remarkable changes observed in the pharmacokinetic profile of drug. Teneligliptin reaches steady state by day 7.

Effect of food: Cmax decreases after a single dose of 20 mg of teneligliptin given after meal to the healthy adults compared to when given in fasting condition and Tmax prolongs up to 2.6 hours; however, no difference observed in AUC.

Distribution: Plasma protein binding of teneligliptin is 77.6 to 82.2%.

Metabolism: Teneligliptin is metabolized in the liver. The most abundant metabolite found in plasma is a thiazolidine-1-oxide derivative (designated as M1, 14.7%). The main enzymes responsible for teneligliptin metabolism are cytochrome P450 (CYP) 3A4 and flavin containing monooxygenase 3 (FMO3), with equal contribution.

Excretion: Of total body clearance, about 34.4% of teneligliptin is excreted unchanged via the kidney and the remaining 65.6% teneligliptin is metabolized and eliminated via renal and hepatic excretion. When a single oral dose of 20 mg teneligliptin was given to the healthy adults, 45.4% of dosage was excreted in urine and 46.5% was excreted in feces up to 216 hours after administration. Mean elimination half-life (t½) of teneligliptin is 24.2 hours. Because of its elimination via multiple pathways, teneligliptin is considered a suitable treatment option for patients with hepatic or renal impairment.

Metformin Sustained Release

Absorption: After an oral dose of the sustained release tablet, metformin absorption is significantly delayed compared to the immediate release tablet with a T_{max} at 7 hours (T_{max} for the immediate release tablet is 2.5 hours). The AUC after a single oral administration of 2000 mg of metformin sustained release tablets is similar to that observed after administration of 1000 mg of metformin immediate release tablets twice daily. The extent of absorption (as measured by AUC) of metformin (in sustained release form) increases when given with food. There was no effect of food on C_{max} and T_{max} of metformin. Both high and low fat meals had the same effect on the pharmacokinetics of metformin in sustained release form.

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 ranged between 63 to 276 liters.

Metabolism: Metformin is excreted unchanged in the urine. No metabolites have been detected in humans.

Excretion: 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 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.

6. Nonclinical Properties

6.1 Animal Toxicology

Teneligliptin

Single Dose Toxicity: Single dose oral administration of teneligliptin in rats - Maximum tolerated dose (MTD) is 1000 mg/kg. Single dose oral administration of teneligliptin in monkeys – MTD is 1000 mg/kg.

Repeated Dose Toxicity: Repeated dose oral administration of teneligliptin in different species from 13 to 52 weeks. For rats, no-observed-adverse-effect levels (NOAELs) were 10 mg/kg (4- and 3-times of maximum recommended human dose - MRHD for male and female respectively), determined by 26-weeks repeated dose toxicity, toxicity including minor high white blood cell counts. A common change in rats and monkeys was histopathological changes in the stomach and intestine.

Genotoxicity: Teneligliptin does not cause genotoxicity. Metabolites M1 and M2 may increase frequency of chromosome structural aberration at 3750 and 3500 μg/ml respectively.

Reproductive and Developmental Toxicity: Fertility toxicity in rats: NOAELs were 70 and 100 mg/kg (11- and 45-times MRHD) for male and female respectively.

Fetal embryonic developmental toxicity: NOAEL was 30 mg/kg (11- and 16-times MRHD for rats and rabbits, respectively).

Postnatal developmental toxicity: NOAEL was 30 mg/kg (11-times MRHD). Teneligliptin distributed to tissues including placenta and fetus in pregnant rats, but the amount of drug in fetus was less than 0.05% of the administered dose.

Carcinogenicity: For rats, NOAELs for tumor were 75 and 100 mg/kg (65- and 76-times MRHD) for male and female respectively. NOAEL for non-neoplastic lesions was 10 mg/kg (76-times MRHD) including changes in lung and kidney.

For mice, NOAEL for tumor was 600 mg/kg (118- and 126-times MRHD for male and female respectively). NOAEL for non-neoplastic lesions was 60 mg/kg (5- and 4-times MRHD for male and female respectively), including localized hyperplasia of squamous epithelium in fore-stomach, diffusion hyperplasia of mucosal epithelium in bladder, diffuse hypertrophy of liver cells, spleen extra-medullary hematopoiesis enhancement, diffuse vacuolation of the bundle meshwork cells in the adrenal gland (males), gallbladder localized hyperplasia of mucosal epithelium (females).

Metformin

Carcinogenesis: 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 3 times the maximum recommended human daily dose of 2550 mg 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.

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.

Impairment of 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 2 times the maximum recommended human daily dose of 2550 mg based on body surface area comparisons.

Teratogenicity: Metformin hydrochloride did not adversely affect development outcomes when administered to pregnant rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 and 5 times a 2550 mg clinical dose based on body surface area comparisons for rats and rabbits, respectively.

7. Description

TENEBLU-M Tablets are white and yellow coloured, elongated, biconvex, bilayered uncoated tablets plain on both the sides.

TENEBLU-M Forte Tablets are white and yellow coloured, biconvex, bilayered uncoated tablets, scored on one side and plain on the other side.

Each tablet of TENEBLU-M contains 20 mg of teneligliptin and 500 mg of metformin hydrochloride (in sustained release form) for oral administration in adults.

Each tablet of TENEBLU-M Forte contains 20 mg of teneligliptin and 1000 mg of metformin hydrochloride (in sustained release form) for oral administration in adults.

Teneligliptin

Teneligliptin is orally acting, pyrrolidine-based inhibitor of dipeptidyl peptidase-4 (DPP-4) enzymes.

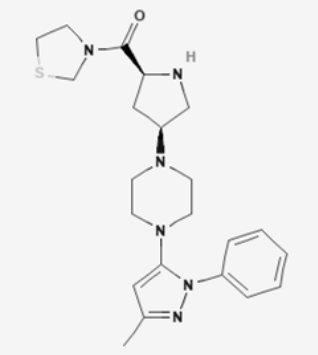
Teneligliptin occurs as a white to off-white powder.

Molecular Weight: 426.6 g/mol.

Molecular Formula: C22H30N6OS.

Chemical Name: [(2S,4S)-4-[4-(5-methyl-2-phenylpyrazol-3-yl)piperazin-1-yl]pyrrolidin-2-yl]-(1,3-thiazolidin-3-yl)methanone.

Structural Formula:



Metformin Hydrochloride

Metformin hydrochloride is the hydrochloride salt of the biguanide metformin with antihyperglycemic effect.

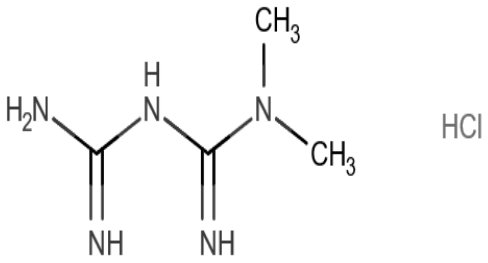
Metformin hydrochloride is white powder which is freely soluble in water and slightly soluble in alcohol.

Molecular Weight: 165.62 g/mol.

Molecular Formula: C4H12ClN5.

Chemical Name: 3-(diaminomethylidene)-1,1-dimethylguanidine;hydrochloride.

Structural Formula:



Inactive ingredients (excipients) of TENEBLU-M Tablet contain Mannitol, Microcrystalline Cellulose, Starch 1500, Low Substituted Hydroxy Propyl Cellulose, Colour Yellow Oxide of Iron, Isopropyl Alcohol, Colloidal Silicon Dioxide, Magnesium Stearate, Hydroxy Propyl Methyl Cellulose, Polyvinyl Pyrrolidone K-30, Mat SR Base - 1, and Talcum.

Inactive ingredients (excipients) of TENEBLU-M Forte Tablet contain Mannitol, Microcrystalline Cellulose, Starch 1500, Low Substituted Hydroxy Propyl Cellulose, Colour Yellow Oxide of Iron, Isopropyl Alcohol, Colloidal Silicon Dioxide, Magnesium Stearate, Hydroxy Propyl Methyl Cellulose, Polyvinyl Pyrrolidone K-30, Mat SR Base – 1, and Talcum.

8. Pharmaceutical Particulars

8.1 Incompatibilities

None known.

8.2Shelf-life
18 months.

8.3Packaging Information
15 tablets per strip.

8.4Storage and Handling Instructions
Store protected from light and moisture at a temperature not exceeding 30°C.
Keep out of the reach of children.

9. Patient Counseling Information
Instructions to Patients

- Instruct patients to take this medicine exactly as prescribed by your doctor. Do not change the dose or stop therapy without consulting your doctor.
- Instruct patients not to take this medicine during pregnancy and lactation unless advised by healthcare professionals.
- Instruct patients not to take this medicine if they have severe liver and/or kidney dysfunction.
- Patients are advised not to take this medicine for type 1 diabetes or for the treatment of diabetic ketoacidosis.
- Instruct patients not to use this medicine during severe infection, surgery, trauma, or if they are seriously dehydrated.
- Advise patients to use this medicine with caution if they have history of abdominal surgery or intestinal obstruction.
- Instruct patients not to take this medicine if they are going to have a contrast x-ray.
- Advise patients not to drink alcohol excessively while on this drug therapy.
- Patients should be advised to take this medicine as an additional therapy to diet and exercise to improve blood sugar levels. Drug therapy is not an alternative or substitute for diet and exercises thus, patients should continue to follow a good lifestyle.

10. Details of Manufacturer
SYNOKEM PHARMACEUTICALS LTD.
Plot No. 56-57, Sector - 6A, I.I.E. Sidcul,
Ranipur, Haridwar – 249403. Uttarakhand.

11. Details of Permission or License Number with Date
TENEBLU-M Tablet: Mfg. Lic. No.: 27/UA/2018; Date of FDA Product Permission: 20/11/2018.

TENEBLU-M FORTE Tablet: Mfg. Lic. No.: 27/UA/2018; Date of FDA Product Permission: 20/11/2018.

12. Date of Revision

April 2021.

Marketed by:
BLUE CROSS LABORATORIES PVT LTD.
A-12, M.I.D.C., NASHIK-422 010.
Regd. Off.: Peninsula Chambers, G. K. Marg, Mumbai-400 013.