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 Tablets IP 20 mg
(Brand Name: TENEBLU® Tablets)

2. Qualitative and Quantitative Composition

Each film-coated tablet contains:
Teneligliptin Hydrobromide Hydrate equivalent to Teneligliptin…….. 20 mg.
Excipients ……... q.s.
Colours: Ferric oxide yellow USP-NF and Titanium Dioxide IP.

3. Dosage Form and Strength

Dosage Form: Tablets.
Dosage Strength: Teneligliptin 20 mg per tablet.

4. Clinical Particulars

4.1 Therapeutic Indication

TENEBLU Tablets are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Usually, teneligliptin is used as monotherapy in patients for whom metformin is inappropriate due to contraindications or intolerance. Further, teneligliptin can also be used in combination with metformin or other antidiabetic medications.
TENEBLU Tablets should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

4.2Posology and Method of Administration

For oral administration in adults.
Recommended dose of teneligliptin is 20 mg to be administered orally once daily without regard to meals. If efficacy is insufficient, the dose may be increased up to 40 mg once daily. TENEBLU Tablet should be swallowed whole with water.
Or, as prescribed by the physician.

4.3Contraindications

TENEBLU Tablets are contraindicated in the following:

- Known hypersensitivity to teneligliptin or to any component of this formulation.

- Type 1 diabetic patients,
- Diabetic coma or history of diabetic coma.
- Severe ketosis.
- Patients with severe infection, surgery, or trauma (preferably insulin to be used to control blood glucose level in these conditions).

4.4Special Warnings and Precautions for Use

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.

4.5Drug Interactions

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 effect (e.g., β-blockers, MAO inhibitors, etc.) or attenuate the blood glucose lowering effect (like steroids, thyroid hormones, etc.).

4.6Use in Special Populations

Pregnant Women

The safety of teneligliptin in pregnant women has not been established. 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.

Lactating Women

It is unknown whether teneligliptin is excreted in human milk. But, animal studies (rat) have shown excretion of teneligliptin in milk. Thus, breast-feeding must be discontinued during administration of this product in lactating women.

Paediatric Patients

Safety and efficacy of teneligliptin in children and adolescents have not been established. Thus, TENEBLU Tablets are not recommended for use in paediatric patients.

Geriatric Patients

Dose adjustments are usually not necessary for elderly patients. But, as elderly patients often have physiological hypofunction, teneligliptin should be administered with caution in them.

Renal Impairment Patients

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. Teneligliptin can be used in diabetes patients with renal impairment, including those on hemodialysis, without the need for dose adjustment.

Hepatic Impairment Patients

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 recommended in mild to moderate hepatic impaired patients. There is no clinical experience of using teneligliptin in severe hepatic dysfunction patients.

4.7Effect on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed. 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 teneligliptin is co-administered with sulphonylurea and/or insulin.

4.8Undesirable Effects

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.

4.9Overdose

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.

5. Pharmacological Properties

5.1 Mechanism of Action

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.

5.2Pharmacodynamic Properties

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.

5.3Pharmacokinetic Properties

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.

6. Nonclinical Properties

6.1 Animal Toxicology

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.

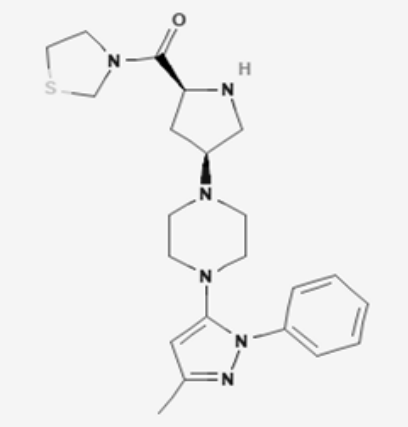
For mice, NOAEL for tumor was 600 mg/kg (118- and 126-times MRHD for male and female respectively). NOAEL for non-neoplastic lesions was 60 mg/kg (5- and 4-times MRHD for male and female respectively), including localized hyperplasia of squamous epithelium in fore-stomach, diffusion hyperplasia of mucosal 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).

7. Description

TENEBLU Tablets are yellow coloured, round, biconvex, film coated tablet.

Each tablet of TENEBLU contains 20 mg of teneligliptin for oral administration.

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:



Inactive ingredients (excipients) of TENEBLU Tablet contain Mannitol, Microcrystalline Cellulose, Starch 1500, Low Substituted Hydroxy Propyl Cellulose, Talcum, Colloidal Silicon Dioxide, Crospovidone, and Magnesium Stearate.

8. Pharmaceutical Particulars

8.1 Incompatibilities

None known.

8.2Shelf-life

24 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 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, or trauma.
- Advise patients to use this medicine with caution if they have history of abdominal surgery or intestinal obstruction.
- 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

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.
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