TEN20-M

1. **Composition**

   Each Tablet Contains

   Teneligliptin 20 mg

   Metformin 500/1000 mg

2. **Dosage form and strength**

Ten 20-M is available in a strip of 10 tablets.

3. **Clinical particulars**

3.1 Therapeutic indication

Type 2 diabetes mellitus

The drug product should be used only in patients who have not sufficiently responded to either of the following treatments.

- Diet and/or exercise therapy alone
- Use of sulfonylureas in addition to diet and/or exercise therapy
- Use of thiazolidinedione in addition to diet and/or exercise therapy.

3.2 Posology and method of administration

As directed by physician.

3.3 Contraindication

Teneligliptin is contraindicated in the following:

- Any patient with a known hypersensitivity to Teneligliptin or any of the components in the formulation,
- Severe ketosis, diabetic coma or history of diabetic coma, type 1 diabetic patients,
- Patients with severe infection, surgery, severe trauma (blood sugar control should preferably be done by insulin).

3.4 Special warnings and precautions for use

Ten 20-M should be administered carefully in the following:

- Patients with advanced liver failure (safety has not been established),

- Patients with congestive heart failure (NYHA category III-IV) (safety has not been established),
- Patients with pituitary insufficiency or adrenal insufficiency, poor nutritional state, starvation, an irregular dietary intake, or debilitating condition, intense muscle movement or excessive alcohol intake (may cause low blood sugar),
- Patients with history of abdominal surgery or with a history of bowel obstruction (may cause bowel obstruction),
- Patients with arrhythmia, severe bradycardia or its history, patients with heart disease such as congestive heart failure or patients with low serum potassium, congenital prolonged QT syndrome, history of Torsades de pointes or patients using antiarrhythmic drugs (may cause QT prolongation),
- Patients using an insulin secretagogue (e.g., sulfonylurea) (risk of severe hypoglycaemia).

3.5 Drug interactions

Teneligliptin should be used with caution with drugs that can enhance the blood glucose lowering effect (like β blockers, MAO inhibitors, etc.) and attenuate the blood glucose lowering effect (like steroids, thyroid hormones, etc). On concomitant therapy with ketoconazole, the geometric least squares mean ratio (concomitant therapy/Teneligliptin monotherapy) of Cmax and AUC0-t of unchanged plasma Teneligliptin with their two-sided 90% CI is 1.37 [1.25, 1.50] and 1.49 [1.38, 1.60], respectively.

- **Cationic drugs:** Certain medications used concomitantly with metformin may increase the risk of lactic acidosis. Cationic drugs that are eliminated by renal tubular secretions (e.g: amiloride, digoxin, morphine, procainamide, quinidine, ranitidine, or vancomycin) may decrease metformin elimination by competing for common renal tubular transport systems. Hence, careful patient monitoring and dose adjustment of metformin/cationic drug is recommended.
- **Furosemide:** A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased the metformin plasma and blood Cmax by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the Cmax and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance.
- **Vitamin B12:** Metformin may result in suboptimal oral vitamin B12 absorption by competitively blocking the calcium dependent binding of the intrinsic factor vitamin B12 complex to its receptor. The reaction very rarely results in pernicious anaemia

which is reversible with discontinuation of metformin and supplementation with vitamin B12.

- **Nifedipine:** Nifedipine appears to enhance the absorption of metformin, it increases plasma metformin Cmax and AUC by 20% and 9% respectively and increases the amount of metformin excreted in the urine.
- **Danazol:** If the use of this active substance cannot be avoided, the patient's urine and blood glucose must be monitored. It may be necessary to adjust the dose of metformin during and after treatment with danazol.

3.6 Use in special population

- Pediatric: Safety and effectiveness in paediatric patients have not been established.
- Geriatric: Safety and effectiveness in paediatric patients have not been established.
- Liver impairment: Teneligliptin should be used with extreme caution in patients with a known history of severe hepatic impairment since the safety and efficacy of this medicine have not been established for such patients. Close monitoring of liver function is recommended in these patients.
- Renal failure: Safety and effectiveness in renal failure patients have not been established.
- Pregnancy and lactation: Teneligliptin should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. Safe use of Teneligliptin during pregnancy has not been established. Teneligliptin should be avoided by breastfeeding mothers (transition to milk has been reported in laboratory animals).

3.7 Effects on ability to drive and use machine

No data available.

3.8 Undesirable effects

The most common adverse reactions reported with Teneligliptin are hypoglycaemia and constipation.

- **Other adverse reactions** reported with Teneligliptin are: Gastrointestinal Disorders: Intestinal obstruction, abdominal bloating, abdominal discomfort, nausea, abdominal pain, flatulence, stomatitis, gastric polyps, colon polyps, duodenal ulcer, reflux esophagitis, diarrhoea, loss of appetite, increased amylase, lipase increased, acute pancreatitis.
- **Kidney and Urinary system:** Proteinuria, urine ketone-positive.
- **Skin and Subcutaneous Tissue Disorders:** Eczema, rash, itching, allergic dermatitis.

- **Investigations:** Increase in AST, ALT, γ-GTP and ALP. Others: Increased CPK, increased serum potassium, fatigue, allergic rhinitis, elevation of serum uric acid.

3.9 Overdose

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 as dictated by the patient's clinical status.

4. Pharmacological properties

4.1 Mechanism of action

- Teneligliptin is a DPP-4 inhibitor, which is believed to exert its actions in patients with type 2 diabetes by slowing the inactivation of incretin hormones. Concentrations of the active intact hormones are increased by Teneligliptin, thereby increasing and prolonging the action of these hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose dependent insulin tropic 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, DPP-4. The incretin 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 signalling pathways involving cyclic AMP. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. By increasing and prolonging active incretin levels, Teneligliptin increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner.
- Metformin improves glucose tolerance in patients with type-2 diabetes (NIDDM), lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Hence, the combination of glimepiride and metformin sustained-release complements each other and provides better glycaemic control in management of type-2 diabetes and probably in the prevention of its associated macrovascular and microvascular complications.

4.2 Pharmacodynamics properties

- Teneligliptin is a long-acting, orally bioavailable, pyrrolidine-based inhibitor of dipeptidyl peptidase 4 (DPP-4), with hypoglycaemic activity. Teneligliptin may also reduce plasma triglyceride levels through a sustained increase in GLP-1 levels.
- Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycaemia in

either patients with type 2 diabetes or normal subjects (except in special circumstances) and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

4.3 Pharmacokinetic properties

After oral administration of a single 20 mg and 40 mg dose to healthy subjects, Teneligliptin was rapidly absorbed, with peak plasma concentrations (mean T max) occurring at 1.8 hours and 1 hour post dose. Plasma AUC of Teneligliptin increased in a dose-proportional manner. Following a single oral 20 mg and 40 mg dose to healthy volunteers, mean plasma AUC of Teneligliptin was 2028.9 and 3705.1 ng*hr/ml, Cmax was 187.2 and 382.4 ng/ml, and apparent terminal half-life (t1/2) was 24.2 and 20.8 hours. Plasma AUC of Teneligliptin increased following 20 mg doses at steady-state compared to the first dose. Co administration with food reduces the Cmax by 20%, increases the Tmax from 1.1 to 2.6 hours but does not affect the AUC of Teneligliptin as compared to that in the fasting state. The plasma protein binding rate is 77.6 – 82.2%. Following a 20 mg single oral dose of [14C] Teneligliptin, 5 metabolites M1, M2, M3, M4 and M5 were observed. In vitro studies indicated that CYP3A4 and flavin-containing monooxygenase (FMO1 and FMO3) are involved in the metabolism of Teneligliptin. Teneligliptin does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C8/9, CYP2C19, and CYP2E1, is a weak inhibitor of CYP2D6, CYP3A4, and FMO (IC50 value : 489.4, 197.5 and 467.2 µmol/l) and does not induce CYP3A4 and CYP1A2. Following a 20 mg single oral dose of [14C] Teneligliptin, 45.4% of administered radioactivity was excreted in urine and 46.5% in faeces till 216 hours after dose. The cumulative urinary excretion rates for up to 120 hours for un-metabolized, M1, M2, and M3 were 14.8%, 17.7%, 1.4% and 1.9% respectively while the cumulative faecal excretion rates for un-metabolized, M1, M3, M4 and M5 were 26.1%, 4.0%, 1.6%, 0.3% and 1.3% respectively. The single administration of Teneligliptin at 20 mg in patients with renal impairment revealed no remarkable changes in Cmax and t1/2 corresponding to the level of renal impairment. Compared with healthy adult subjects, the AUC of subjects with mild renal impairment (50 ≤ creatinine clearance [Ccr] ≤ 80 mL/minute), moderate renal impairment (30 ≤ Ccr < 50 mL/minute), and severe renal impairment (Ccr < 30 mL/minute) was approximately 1.25 times, 1.68 times, and 1.49 times higher than that of healthy adult subjects, respectively. A single administration of Teneligliptin 20 mg in patients with hepatic impairment revealed that the Cmax of subjects with mild hepatic impairment (Child–Pugh classification: total score 5–6) and moderate hepatic impairment (Child–Pugh classification: total score 7–9) was approximately 1.25 times and 1.38 times that of healthy adult subjects, respectively. Compared to healthy adult subjects, the AUC of subjects with mild and moderate hepatic impairments was approximately 1.46 times and 1.59 times higher than that of healthy adult subjects, respectively. There have been no previous clinical studies

using Teneligliptin in patients with severe hepatic impairment (Child–Pugh classification: total score was greater than 9).

Metformin hydrochloride is slowly and incompletely absorbed from the gastrointestinal tract; the absolute bioavailability of a single 500-mg dose is reported to be about 50 to 60%, although this is reduced somewhat if taken with food. Once absorbed, protein binding in plasma is negligible; the drug is excreted unchanged in the urine. The plasma elimination half-life is reported to range from about 2 to 6 hours after oral doses. Metformin crosses the placenta and is distributed into breast milk in small amounts.

5. Nonclinical properties

5.1 Animal Toxicology or Pharmacology

Not required.

6. Description

Already mentioned and covered in the above points.

7. Pharmaceutical particulars

7.1 Incompatibilities

There are no known incompatibilities.

7.2 Shelf-life

24 months.

7.3 Storage and handling instructions

Store below 25^{o}C away from direct sunlight, heat and moisture.