SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

1.1 Invented Name of the Medicinal Product

TILYPTIN-20

1.2 Strength

20 mg

2. QUALITATIVE AND QUANTITAVE COMPOSITION

Each film coated tablet contains:
Teneligliptin Hydrobromide Hydrate
equivalent to Teneligliptin 20 mg

3. PHARMACEUTICAL FORM

Tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications :

Type 2 diabetes mellitus:
The drug product should be used only in patients who have not sufficiently responded to either of the following treatments.
(a) Diet and/or exercise therapy alone
(b) Use of sulfonylureas in addition to diet and/or exercise therapy
(c) Use of thiazolidinedione’s in addition to diet and/or exercise therapy

4.2 Posology and method of administration:

The usual adult dosage is 20 mg of Teneligliptin administered orally once daily. If efficacy is insufficient, the dose may be increased up to 40 mg once daily while closely monitoring the clinical course.

4.3 Contraindications :

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).

4.4 Special warnings and precautions for use:

Teneligliptin 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).

4.5 Interaction with other medicinal products and other forms of interaction.

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.

4.6 Pregnancy and lactation

Teneligliptin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. 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).

Safety and effectiveness of Teneligliptin in pediatric patients have not been established.

4.7 Effects on ability to drive and use machines

Not Known

4.8 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

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties:

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 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. By increasing and prolonging active Incretin levels, Teneligliptin increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner.

5.2 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. Coadministration 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 monooxygenases (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 AUC0–∞ 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 AUC0–∞ 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).

5.3 Preclinical safety data:

Teneligliptin (0 [vehicle], 100, 300, 1000 mg/kg/day) was administered orally to Wistar rats (3 each of males and females per group) for 2 weeks. In the 1000 mg/kg/day group, all animals died or sacrificed moribund and necropsied on Day 5 of administration. In the 300 mg/kg/day group, 2 males and all females were sacrificed moribund and necropsied from Day 7 to 14 of administration. These animals showed hyperplasia of esophageal and periventricular mucosal epithelium, hyperkeratosis, sub mucosal infiltration of inflammatory cells, disappearance, decrease, or swelling of parietal cells in the glandular stomach, erosion of intestinal mucosa, single-cell death in mucosal epithelium, single-cell death of hepatocytes in the liver, bile duct proliferation, basophilic change and hypertrophy of the tubular epithelium in the outer zone of renal medulla, decrease in lymphocytes in the periarterial lymphatic sheath (PALS) of the spleen, bone marrow congestion, and foamy alveolar macrophages.

In bacterial reverse mutation tests, in bone marrow micronucleus tests in rats after oral administration, and in unscheduled DNA synthesis test in liver cells, Teneligliptin was negative for genotoxicity. In a chromosomal aberration test with cultured mammalian cells, the frequency of cells with abnormal structure increased after treatment with 2250 and 2500 μg/mL of Teneligliptin for 6 hours in the absence of metabolic activation system. However, since the cell growth index at these concentrations was only 29% and 19%, respectively, from which the applicant considers that the changes were secondary to cytotoxicity. From these results, the applicant has determined that Teneligliptin is not genotoxic.

Teneligliptin (0 [vehicle], 10, 25, 75 mg/kg/day in males and 0 [vehicle], 10, 30, 100 mg/kg/day in females) was administered to Wistar rats (55 each of males and females per group) for 104

weeks. Administration of Teneligliptin did not cause any increase in neoplastic lesion. The number of animals with anterior pituitary adenoma or those with fibro adenoma of breast (females only) decreased in males of the 75 mg/kg/day group and in females of the 100 mg/kg/day group compared with the control group. Non-neoplastic lesions observed were mineralization of renal papilla and pelvis epithelium in males of the ≥25 mg/kg/day groups, hyperplasia of thymic epithelium in females of the ≥30 mg/kg/day groups, increased number of animals with foamy alveolar macrophages in males of the 75 mg/kg/day group and in females of the 100 mg/kg/day group, and increased frequency of renal tubular casts and chronic progressive nephropathy in females of the 100 mg/kg/day group. From these results, the NOAEL was determined to be 75 mg/kg/day in males and 100 mg/kg/day in females for neoplastic changes, and 10 mg/kg/day in both males and females for non-neoplastic changes. The AUC0-24 h at Week 52 was 17,400 and 16,100 ng·h/mL, respectively, in males and females of the 10 mg/kg/day group, 237,000 ng·h/mL in the 75 mg/kg/day group, and 278,000 ng·h/mL in the 100 mg/kg/day group, which was 4.8, 4.4, 65.3, and 76.6 times, respectively, the clinical exposure level.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months from the date of manufacturing.

6.4 Special precautions for storage

Store below 30°C. Protect from light. Keep out from the reach of children.

6.5 Nature and contents of container

Alu - Alu Blister pack of 10 tablets, 3 such blisters in a carton along with pack Insert.

7. Marketing Authorization Holder

Manufactured by:

MICRO LABS LIMITED

92, SIPCOT INDUSTRIAL COMPLEX

HOSUR, TAMIL NADU – 635126, INDIA

8. Marketing Authorization Number

Not applicable

9. Date of first authorization/renewal of authorization

Not applicable

10. Date of revision of text

April 2017