National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS

TENELISIGN
(Teneligliptin Tablets 20 mg)

1. NAME OF THE MEDICINAL PRODUCT

Teneligliptin Tablets 20 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Teneligliptin Hydrobromide Hydrate	
Eq. to Teneligliptin	20 mg
Excipients	q.s.
Colour: Titanium Dioxide IP	

3. PHARMACEUTICAL FORM

Film coated tablet

4. CLINICAL PARTICULARS

4.1Therapeutic indications:

Monotherapy:

TENELISIGN Tablets is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus.

Combination therapy:

TENELISIGN Tablets is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin, sulfonylureas, PPAR agonist (e.g., thiazolidinediones), rapid insulin secretagogues, alpha-glucosidase inhibitors, sodium glucose co-transporter 2 inhibitor, or insulin when the single agent alone, with diet and exercise, does not provide adequate glycemic control.

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 to 40 mg once daily with close monitoring of clinical course.

4.3Contraindication:

TENELISIGN Tablets is contraindicated in the following patients.

1) Patients with a history of hypersensitivity to any of the ingredients of this product.

2) Patients with severe ketosis, diabetic coma or precoma, and type 1 diabetes mellitus [Treatment with this product is not appropriate because such patients require rapid correction of hyperglycaemia with transfusion and insulin.]

3) Patients with severe infection, pre- or post-operative patients, and patients with serious traumatic 2 injury [Treatment with this product is not appropriate because glycaemic control with insulin injection is desirable in such patients.]

4.4 Special warnings and precautions for use

Careful Administration

TENELISIGN Tablets should be administered with care in the following patients.

Patients with severe hepatic impairment [There has been no clinical experience establishing its safety in such patients.

Patients with cardiac failure (NYHA class III or IV) [There has been no clinical experience establishing its safety in such patients.

Patients receiving sulfonylurea or insulin [The risk of hypoglycaemia may be increased.

The following patients or conditions [Hypoglycaemia may occur.]

- Pituitary insufficiency or adrenal insufficiency
- Malnutrition, starvation, irregular diet, insufficient food intake or hyposthenia
- Extreme muscle exercise
- Patients with excessive alcohol intake

Patients with a history of abdominal operation or a history of intestinal obstruction [Intestinal obstruction may occur.

Patients prone to QT interval prolongation (patients with current or a history of arrhythmia such as severe bradycardia, patients with cardiac disease such as congestive cardiac failure, patients with hypokalaemia, etc.) [QT interval prolongation may occur.]

Important Precautions

1) Prior to the use of this product, patients should be instructed to recognize hypoglycemic symptoms and their management. In particular, when used in combination with sulfonylurea or insulin, this product may increase the risk of hypoglycaemia. In order to decrease the risk of hypoglycaemia associated with coadministration with sulfonylurea or insulin, a reduction in the dose of sulfonylurea or insulin should be considered when this product is coadministered with these drugs.

2) Use of this product should be considered only in patients with established diagnosis of diabetes mellitus. It should be noted that there are other diseases than diabetes mellitus that have symptoms similar to those of diabetes mellitus (renal glycosuria, abnormal thyroid function, etc.), such as impaired glucose tolerance and positive urine sugar.

3) Use of this product should be considered only when there is inadequate response to diet and exercise therapy, which are fundamental for treatment of diabetes mellitus, after adequate trial of the therapies.

4) During treatment with this product, blood glucose should be regularly monitored, and the effect of the drug should be checked. If the response to this product is inadequate after 3 months of treatment, a change to other treatment should be considered.

5) During continued treatment with this product, it may become unnecessary to administer the product or it may become necessary to reduce a dose of the product. In addition, there may be no or inadequate response to the product due to patient's failure to take care of themselves or a complication of infection, etc. Therefore, attention should be paid to the amount of food intake, blood glucose level and presence/absence of infection to judge continuation of treatment, doses and selection of drugs.

6) Adverse drug reactions such as prolonged QT may occur. Treatment with this product should preferably be avoided in patients with current or a history of QT interval prolongation (congenital long QT syndrome, etc.) or with a history of Torsades de pointes.

7] Both GLP-1 receptor agonists and this product have an antihyperglycaemic action mediated by GLP-1 receptor. No results of clinical trials studying a combined therapy with both drugs are available and the efficacy and safety of the coadministration have not been proved.

8) Acute pancreatitis may occur. Patients should be instructed to consult with a physician immediately 3 if initial symptoms including persistent and intense abdominal pain and/or vomiting occur.

<u>Use in the Elderly</u>

Since elderly patients often have reduced physiological function, this product should be administered carefully with close monitoring of the patient's condition.

<u>Paediatric Use</u> The safety of this product in low-birth-weight infants, neonates, nursing infants, infants, or children has not been established (no clinical experience).

<u>Precaution concerning Use</u> For drugs that are dispensed in a press-through package (PTP), instruct the patient to remove the drug from the PTP sheet prior to use. [It was reported that, if the PTP sheet is swallowed, the sharp corners of the sheet may puncture the esophageal mucosa, resulting in severe complications such as mediastinitis.]

<u>Other Precautions</u> QT interval prolongation has been reported after administration of this product at a dose of 160 mg once daily. [The usual approved dosage of this product is 20 mg of Teneligliptin once daily, and the maximum dosage is 40 mg once daily]

4.5 Interaction with other medicinal products and other forms of interaction

Drugs for diabetes mellitus Sulfonylurea Rapid-acting insulin secretagogues Alpha-glucosidase inhibitors Biguanides, Thiazolidines GLP-1 receptor agonists SGLT2 inhibitors Insulin, etc.

When this product is coadministered, patients should be carefully observed since hypoglycemic symptoms may occur. In particular, when used in combination with sulfonylurea or insulin, the risk of hypoglycaemia may be increased. In order to decrease the risk of hypoglycaemia associated with coadministration with sulfonylurea or insulin, a reduction in the dose of sulfonylurea or insulin should be considered. When hypoglycemic symptoms appear, sucrose should normally be administered. When this product is coadministered with an alpha-glucosidase inhibitor, glucose should be administered.

Drugs that intensify antihyperglycaemic action Beta-blockers Salicylic acid Monoamine oxidase inhibitors, etc.

When this product is coadministered, blood glucose level and patient's other conditions should be carefully observed since blood glucose may further be decreased.

Drugs that reduce antihyperglycaemic action Adrenalin Adrenocortical hormones Thyroid hormones, etc.

When this product is coadministered, blood glucose level and patient's other conditions should be carefully observed since blood glucose may be increased.

Drugs that are known to cause QT interval prolongation

Class IA antiarrhythmic (quinidine sulfate hydrate, procainamide hydrochloride, etc.) Class III antiarrhythmic (amiodarone hydrochloride, sotalol hydrochloride, etc.)

When this product is coadministered, QT interval prolongation, etc. may occur.

4.6 Fertility, pregnancy and lactation General principles

Pregnancy

This product should be used in pregnant women or women who may possibly be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment. [The safety of this product for use during pregnancy has not been established. An animal study (in rats) has reported that this product is transferred to the fetus.]

Breast-feeding

In lactating women, breast-feeding must be discontinued during treatment. [An animal study (in rats) has reported that this product is excreted in breast milk.]

4.7 **Effects on ability to drive and use machines**

Since hypoglycemic symptoms may occur, attention should be paid to patients engaged in work at altitude or driving a car, etc.

4.8 Undesirable effects

Clinically significant adverse drug reactions

1) Hypoglycaemia (1.1–8.9%): Hypoglycaemia may occur with coadministration of this product with other drugs for diabetes mellitus. In particular, some cases of serious hypoglycemic symptoms that resulted in loss of consciousness have been reported in coadministration with insulin products or sulfonylurea. Dose reduction of insulin products or sulfonylurea should be considered when this product is coadministered with these drugs. Hypoglycaemia has also been reported with this product when not coadministered with other drugs for diabetes mellitus. If hypoglycemic symptoms are observed, appropriate therapeutic measures, such as intake of sugar-containing food, should be taken.

2) Intestinal obstruction (0.1%): Intestinal obstruction may occur. The patient should be carefully 5 monitored, and if any abnormalities, such as severe constipation, abdominal distension, persistent abdominal pain and vomiting, are observed, this product should be discontinued and appropriate therapeutic measures should be taken.

3) Hepatic impairment (incidence unknown): Hepatic impairment accompanied by increased AST (GOT) or ALT (GPT) may occur. The patients should be carefully monitored, and if any

abnormalities are observed, appropriate therapeutic measures including discontinuation of administration should be taken.

4) Interstitial pneumonia (incidence unknown): Interstitial pneumonia may occur. If any abnormalities, such as cough, dyspnoea, pyrexia and lung crepitation, are observed, laboratory tests including chest X-ray, chest CT, serum marker, etc. should be promptly performed. If interstitial pneumonia is suspected, this product should be discontinued and appropriate therapeutic measures including administration of corticosteroids should be taken.

5) Pemphigoid (incidence unknown): Pemphigoid may occur. If blister, erosion, or other signs and symptoms are observed, patients should be referred to a dermatologist, and appropriate therapeutic measures such as discontinuation of administration should be taken.

6) Acute pancreatitis (incidence unknown): Acute pancreatitis may occur. Patients should be instructed to consult with a physician immediately if initial symptoms including persistent and intense abdominal pain and/or vomiting occur.

Other adverse drug reactions

If any adverse drug reactions are observed, appropriate therapeutic measures, such as discontinuation of this product, should be taken.

Incidence / Type	≥0.1% to<1%	<0.1%	Incidence unknown
Psychiatric/ Neurological			Dizziness
Gastrointestinal	Constipation, abdominal distension, abdominal discomfort, nausea, abdominal pain, flatulence, stomatitis, gastric polyps, colonic polyp, duodenal ulcer, reflux esophagitis, diarrhoea, decreased appetite, increased amylase, increased lipase		
Hepatic	Increased AST (GOT), increased ALT (GPT), increased γ-GTP	Increased Al-P	
Renal/ Urinary system	Proteinuria, urine ketone body present, blood urine present		
Dermatologic	Eczema, rash, itching, allergic dermatitis		
Others	Increased serum CK (CPK), increased serum potassium, malaise, allergic rhinitis, increased serum uric acid		Peripheral oedema

4.9 Overdose

The maximum doses of Teneligliptin in clinical studies were 320 mg for a single dose in healthy adult subjects and 80 mg once daily for 7 days for repeated doses in healthy adult subjects. No serious adverse drug events and adverse drug events leading to discontinuation of the study treatment were reported after administration of Teneligliptin at the 2 doses. QT interval prolongation has been reported after administration of this product at a dose of 160 mg once daily.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties:

Mechanism of action

Glucagon-like peptide-1 (GLP-1) is secreted from the gastrointestinal tract in response to meal ingestion and regulates postprandial blood glucose level by stimulating insulin

secretion from the pancreas and suppressing glucagon secretion. Teneligliptin inhibits the degradation of GLP-1 through the inhibition of dipeptidyl peptidase-4 (DPP-4) and reduces blood glucose levels by increasing blood concentration of active GLP-1.

Inhibitory effect on DPP-4 and suppressive action on GLP-1 degradation

1) Teneligliptin inhibited the activity of DPP-4 in human plasma in a concentration-dependent manner, with IC50 of 1.75 nmol/L (in vitro).

2) Teneligliptin prevented the degradation of active GLP-1 in rat plasma in a concentration-dependent manner (in vitro).

3) In a glucose tolerance test in Zucker Fatty rats, a model of obesity with insulin resistance and impaired glucose tolerance, a single oral administration of Teneligliptin increased plasma active GLP-1 and plasma insulin levels.

4) In patients with type 2 diabetes mellitus, once-daily administration of Teneligliptin 20 mg inhibited plasma DPP-4 activity and increased the concentration of active GLP-1 in plasma.

Improvement of glucose tolerance

1) In a glucose tolerance test in Zucker Fatty rats, a model of obesity with insulin resistance and impaired glucose tolerance, a single oral administration of Teneligliptin improved post-loaded hyperglycemia.

2) In patients with type 2 diabetes mellitus, once-daily administration of Teneligliptin 20 mg improved blood glucose after breakfast, lunch and dinner and fasting blood glucose.

5.2 Pharmacokinetic properties:

Plasma protein binding The in vitro protein bindings of 14C-labeled teneligliptin (20, 100 and 500 ng/mL) to human plasma were 77.6% to 82.2%.

Metabolism

1) When healthy adults (n = 6) were administered a single oral dose of 14C-labeled teneligliptin 20 mg, the unchanged drug and its metabolites, M1, M2, M3, M4 and M5, were found in plasma. The AUC0-∞ ratios of Teneligliptin and its metabolites M1, M2, M3, M4 and M5 to total radioactivity, which were calculated based on plasma radioactive concentrations up to 72 hours after administration, were 71.1%, 14.7%, 1.3%, 1.3%, 0.3% and 1.1%, respectively.

2) CYP3A4 and flavin-containing monooxygenase (FMO1 and FMO3) are primarily involved in metabolism of Teneligliptin. While Teneligliptin had weak inhibitory effect on CYP2D6, CYP3A4 and FMO (IC50: 489.4, 197.5 and 467.2 μmol/L, respectively), it had no inhibitory effect on CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C8/9, CYP2C19 and CYP2E1 and did not induce CYP1A2 and CYP3A4 (in vitro).

Excretion

1) When healthy adults were administered a single oral dose of 20 mg and 40 mg of Teneligliptin under fasting condition (n = 6 each), 21.0% to 22.1% of the administered dose was excreted unchanged drug in the urine, and renal clearance was 37 to 39 mL/hr/kg.

2) When healthy adults (n = 6) were administered a single oral dose of 14C-labeled Teneligliptin 20 mg, 45.4% and 46.5% of the administered radioactive dose was excreted in the urine and feces, respectively. Cumulative urinary excretion of unchanged drug, M1, M2 and M3 to the doses up to 120 hours after administration was 14.8%, 17.7%, 1.4% and 1.9%, respectively, and cumulative fecal excretion of unchanged drug, M1, M3, M4 and M5 was 26.1%, 4.0%, 1.6%, 0.3% and 1.3%, respectively.

3) Teneligliptin is a substrate of P-glycoprotein and inhibited digoxin transport mediated by Pglycoprotein to 42.5% at a concentration of 99 μmol/L. In addition, while teneligliptin had weak inhibitory effect on organic anion transporter (OAT) 3 expressed in the kidney (IC50: 99.2 μmol/L), it had no inhibitory effect on OAT 1, organic cation transporter (OCT) 2, organic anion-transporting polypeptide (OATP) 1B1 and OATP 1B3 (in vitro).

5.3 Preclinical safety data:

In a 52-week repeated oral dose toxicity study in cynomolgus monkeys, skin lesions including exfoliation, scab and ulcer were observed on the tail, extremities and/or auricle at a dose of 75 mg/kg/day. AUC0-24hr when the lesions were observed reached approximately 45 times that in humans treated with 40 mg/day. The same toxicity findings have not been reported in other animal species (rats, mice and rabbits) and humans. Teneligliptin was negative for genotoxicity in an in vitro bacterial reverse mutation test and in vivo micronucleus and unscheduled DNA synthesis tests in rats, although it was positive in an in vitro chromosomal aberration test due to secondary effects of cytotoxicity. Therefore, it is concluded that Teneligliptin shows no genotoxicity. Teneligliptin showed no carcinogenic potential in a 2-year carcinogenicity study in rats and a 26-week carcinogenicity study in transgenic mice. In a fertility and early embryonic development study in rats, low body weight gain, decreased implantations and live embryos, and secondary changes in male reproductive organs due to low body weight gain were observed. In embryo-fetal development studies in rats and rabbits, skeletal variations and decreased ossifications were observed in fetuses, but no signs suggesting teratogenicity were noted. In a pre- and post-natal development study in rats, a slightly low body weight gain was observed in offspring. AUC0-24hr at the NOAELs in reproductive and developmental toxicity studies reached more than 10 times that in humans treated with 40 mg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

Microcrystalline Cellulose, Starch, Hydroxy Propyl Methyl Cellulose, Purified water, Aerosil (Colloidal Anhydrous Silicon Dioxide), L-Substituted HPC (LH -11), Magnesium Stearate, P.E.G- 400, Talcum, Titanium Dioxide, Isopropyl Alcohol, Methelene Dichloride

6.2 Incompatibilities: NONE

6.3 Shelf life:

30 months from the date of manufacture.

6.4 Special precautions for storage:

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container:

Pack of 10X15 Tablets

6.6 Special precautions for disposal and other handling:

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESSES

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