TENELIA®

teneligliptin hydrobromide hydrate

Mitsubishi Tanabe Pharma

Summary of Product Characteristic

1. NAME OF THE MEDICINE PRODUCT

TENELIA® 20 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

(INN: Teneligliptin)

TENELIA® 20 mg Tablets

Each tablet contains 31 mg teneligliptin hydrobromide hydrate equivalent to 20 mg teneligliptin.

3. PHARMACEUTICAL FORM

Tablets are light red, film-coated and round-shaped. Tablet size and weight are as follows: Diameter 7.1 mm, Thickness 3.1 mm, Weight 125 mg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Monotherapy:
TENELIA® is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus

Combination therapy:
TENELIA® 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.

4.3 Contraindications

TENELIA® 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

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

TENELIA® should be administered with care in the following patients.

1) Patients with severe hepatic impairment [There has been no clinical experience establishing its safety in such patients (see section 5.2).]
2) Patients with cardiac failure (NYHA class III or IV) [There has been no clinical experience establishing its safety in such patients.]
3) Patients receiving sulfonylurea or insulin [The risk of hypoglycaemia may be increased (see "Important Precautions" of this section, sections 4.5 and 4.8).]
4) 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
5) Patients with a history of abdominal operation or a history of intestinal obstruction [Intestinal obstruction may occur (see section 4.8).]
6) 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 (see section 4.9 and 5.2).]

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 (see "Careful Administration" of this section, sections 4.5 and 4.8).
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 (see section 4.9 and 5.2).
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

if initial symptoms including persistent and intense abdominal pain and/or vomiting occur(see section 4.8).

Use in the Elderly

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

Pediatric Use

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

Precaution concerning Use

<Precautions regarding dispensing>
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.]

Other Precautions

QT interval prolongation has been reported after administration of this product at a dose of 160 mg once daily (see section 4.9 and 5.2). [The usual approved dosage of this product is 20 mg of teneligliptin once daily, and the maximum dosage is 40 mg once daily (see section 4.2).]

4.5 Interactions with other medicinal products and other forms of interactions

This product is primarily metabolized by CYP3A4 and flavin-containing monooxygenase (FMO1 and FMO3), and urinary excretion of unchanged drug was 14.8% to 22.1% (see section 5.2).

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
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 (see sections 4.4 and 4.8). When hypoglycemic symptoms appear, sucrose should normally be administered. When this product is coadministered with an alpha-glucosidase inhibitor, glucose should be administered.	Antihyperglycaemic action is intensified.

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
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.	Antihyperglycaemic action is intensified.
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.	Antihyperglycaemic action is reduced.
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.	These drugs are associated with QT interval prolongation even when administered alone.

4.6 Fertility Pregnancy and Lactation

1) 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.]
2) 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

In Japanese clinical studies, 232 adverse drug reactions (including abnormal laboratory values) were observed in 156 patients (9.5%) of total 1645 patients. Main adverse drug reactions were hypoglycaemia in 43 patients (2.6%) and constipation in 14 patients (0.9%).

<u>Clinically significant adverse drug reactions</u>

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 (see sections 4.4 and 4.5).
2) Intestinal obstruction (0.1%): Intestinal obstruction may occur. The patient should be carefully

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 (see section 4.4).

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. (see section 4.4)

Other adverse drug reactions

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

Type \ Incidence	≥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		
Musculoskeletal			Arthralgia
Others	Increased serum CK (CPK), increased serum potassium, malaise, allergic rhinitis, increased serum uric acid		Peripheral oedema

The frequency of adverse drug reactions was calculated based on the clinical trial.

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 (see section 4.4 and 5.2).

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 IC_{50} 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.

Clinical efficacy

Monotherapy

1) Placebo-controlled double-blind comparative study (dose-finding study)

Patients with type 2 diabetes mellitus inadequately controlled on diet and exercise therapy received 10 mg, 20 mg or 40 mg of teneligliptin or placebo once daily for 12 weeks. The difference (Least mean square value [95% confidence interval]) from the placebo group of the change in HbA1c level from baseline at Week 12 was -0.90 [-1.06, -0.75]% in the 20 mg administration group (n = 79), and -1.01 [-1.16, -0.86]% in the 40 mg administration group (n = 81). The incidence of adverse drug reaction of hypoglycaemia was 0% (0/79 patients) in the 20 mg administration group and 3.7% (3/81 patients) in the 40 mg administration group. (The usual dosage of this drug is 20 mg once daily, as teneligliptin, and the maximum approved dosage is 40 mg once daily.)

2) Placebo-controlled double-blind comparative study (confirmatory study)

Patients with type 2 diabetes mellitus inadequately controlled on diet and exercise therapy (n = 203) received 20 mg of teneligliptin or placebo once daily for 12 weeks. The result is shown in the following table. No adverse drug reaction of hypoglycaemia was observed in the teneligliptin-treated group.

Table: Results of the placebo-controlled double-blind comparative study (at Week 12)

	Change from baseline		
	Placebo n = 104	Teneligliptin n = 99	Difference between groups
HbA1c (%)	0.17 ± 0.05	-0.62 ± 0.05	-0.79* [-0.94, -0.64]
Fasting blood glucose (mg/dL)	-0.2 ± 1.8	-19.2 ± 1.8	-19.0* [-24.0, -13.9]
Blood glucose 2 hours after meals (mg/dL)	-3.2 ± 3.6	-47.9 ± 3.5	-44.7* [-54.6, -34.8]

Least square mean ± SE; *p<0.0001; two-sided 95% confidence interval in brackets.

Combination therapy with other hypoglycemic agents

1) Combination therapy with sulfonylurea

Patients with type 2 diabetes mellitus inadequately controlled on diet and exercise therapy and glimepiride (n = 194) received 20 mg of teneligliptin or placebo once daily for 12 weeks. The result is shown in the following table.

Table: Results of the combination study with glimepiride (at Week 12) (placebo-controlled double-blind comparative combination study)

	Change from baseline		
	Placebo group (Glimepiride monotherapy) n = 98	Teneligliptin 20 mg group (Glimepiride combination therapy) n = 96	Difference between groups
HbA1c (%)	0.29 ± 0.06	-0.71 ± 0.06	-1.00* [-1.16, -0.84]

Least square mean ± SE; *p<0.0001; two-sided 95% confidence interval in brackets.

When patients received the dose of 20 mg or 40 mg (when the dose was increased) once a day with glimepiride after Week 12, the change (mean ± SD) in HbA1c level from baseline at Week 52 was -0.56 ± 0.87% (n = 96). The incidence of adverse drug reaction of hypoglycaemia up to Week 52 was 7.3% (7/96 patients).

2) Combination therapy with thiazolidine

Patients with type 2 diabetes mellitus inadequately controlled on diet and exercise therapy and pioglitazone (n = 204) received 20 mg of teneligliptin or placebo once daily for 12 weeks. The result is shown in the following table.

Table: Results of the combination study with pioglitazone (at Week 12) (placebo-controlled double-blind comparative study)

	Change from baseline		
	Placebo group (Pioglitazone monotherapy) n = 101	Teneligliptin 20 mg group (Pioglitazone combination therapy) n = 103	Difference between groups
HbA1c (%)	-0.20 ± 0.05	-0.94 ± 0.04	-0.74* [-0.87, -0.62]

Least square mean ± SE; *p<0.0001; two-sided 95% confidence interval in brackets.

When patients received the dose of 20 mg or 40 mg (when the dose was increased) once a day with pioglitazone after Week 12, the change (mean ± SD) in HbA1c level from baseline at Week 52 was -0.86 ± 0.66% (n = 103). The incidence of adverse drug reaction of hypoglycaemia up to Week 52 was 1.9% (2/103 patients).

3) Combination therapy with insulin

Patients with type 2 diabetes mellitus inadequately controlled on insulin monotherapy (mixed type [short-acting or rapid-acting type insulin content 25% or 30%], intermediate type, or long-acting type at a daily dose of 8 units or more but 40 units or less) in addition to diet and exercise therapy (n =148) received 20 mg of teneligliptin or placebo once daily for 16 weeks. The result is shown in the following table.

Table: Results of combination study with insulin (at week 16)

	Change from baseline		
	Placebo group (Insulin monotherapy) n = 71	Teneligliptin 20 mg group (Insulin combination therapy) n = 77	Difference between groups
HbA1c (%)	-0.07 ± 0.08	-0.87 ± 0.08	-0.80* [-1.02, -0.58]

Least square mean ± SE; *p<0.001; two-sided 95% confidence interval in brackets.

When patients received the dose of 20 mg or 40 mg (when the dose was increased) once a day with insulin after Week 16, the change (mean ± SD) in HbA1c level from baseline at Week 52 was -0.81 ± 0.93% (n = 77). The incidence of adverse drug reaction of hypoglycaemia up to Week 52 was 15.6% (12/77 patients).

Long-term study (monotherapy and combination therapy with glinide, biguanide, or α-glucosidase inhibitor)

Patients with type 2 diabetes mellitus inadequately controlled on glinide, biguanide, or an α-glucosidase-inhibitor in addition to dietary and exercise therapy (n = 462) received 20 mg or 40 mg (when the dose was increased) of teneligliptin once daily for 52 weeks. The change in HbA1c level from baseline at Week 52 was -0.63 ± 0.64% (n = 212) in monotherapy, -0.76 ± 0.70% (n = 80) in combination with glinide, -0.78 ± 0.75% (n = 95) in combination with biguanide, and
-0.89 ± 0.64% (n = 75) in combination with an α-glucosidase inhibitor. The incidence of adverse drug reactions of hypoglycaemia up to Week 52 was 1.4% (3/212 patients) in monotherapy, 3.8% (3/80 patients) in combination with glinide, 1.1% (1/95 patients) in combination with biguanide, and 1.3% (1/75 patients) in combination with an α-glucosidase inhibitor.

5.2 Pharmacokinetic properties

Plasma concentrations

1) Single administration

Plasma concentration–time profiles of teneligliptin and its pharmacokinetic parameters after single oral administration of 20 mg and 40 mg of teneligliptin to healthy adults under fasting condition are as shown below.

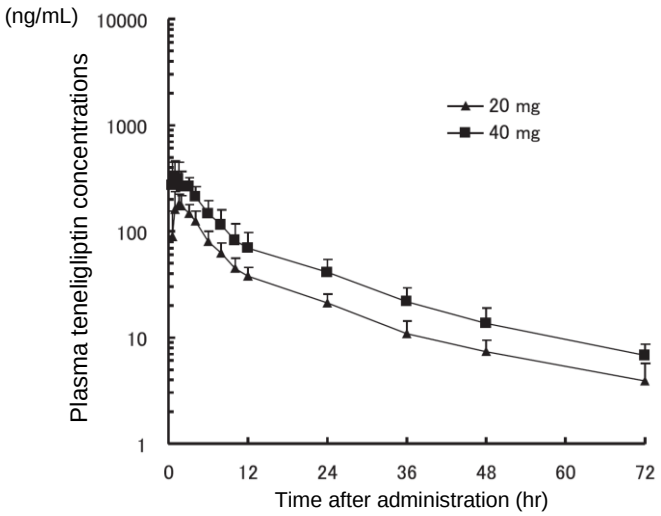

Figure: Plasma concentration–time profiles of teneligliptin after single oral administration in healthy adults (mean + SD; n = 6)

Table: Pharmacokinetic parameters of teneligliptin after single oral administration in healthy adults

	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	t_{max} (hr)	$t_{1/2}$ (hr)
20 mg	187.20 ± 44.70	2028.9 ± 459.5	1.8 (1.0-2.0)	24.2 ± 5.0
40 mg	382.40 ± 89.83	3705.1 ± 787.0	1.0 (0.5-3.0)	20.8 ± 3.2

n = 6; Mean ± SD, t_{max}: Median (min-max), $t_{1/2}$: Terminal elimination half-life

2) Repeated administration

The pharmacokinetic parameters of teneligliptin after repeated oral administration of 20 mg of teneligliptin once daily for 7 days to healthy adults 30 minutes before breakfast are as shown below and were estimated to reach steady state within 7 days.

Table: Pharmacokinetic parameters of teneligliptin after repeated oral administration in healthy adults

	C_{max} (ng/mL)	AUC_{0-24hr} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	t_{max} (hr)	$t_{1/2}$ (hr)
After initial dose	160.60 ± 47.26	1057.2 ± 283.9	1627.9 ± 427.8	1.0 (0.4-2.0)	25.8 ± 4.9
After 7 days of treatment	220.14 ± 59.86	1514.6 ± 370.5	2641.4 ± 594.7	1.0 (1.0-1.0)	30.2 ± 6.9

n = 7; Mean ± SD, t_{max}: Median (min-max), $t_{1/2}$: Terminal elimination half-life

3) Effects of food

When healthy adults were administered a single oral dose of 20 mg of teneligliptin after meals, there was a 20% decrease in C_{max} compared to under fasting condition and a prolongation in t_{max} from 1.1 hours to 2.6 hours, while there was no difference in AUC.

Table: Pharmacokinetic parameters of teneligliptin after administration under fasting condition and after meals in healthy adults

	C_{max} (ng/mL)	AUC_{0-72hr} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	t_{max} (hr)	$t_{1/2}$ (hr)
Under fasting condition	232.2 (236.2 ± 43.77)	1855.5 (1861.1 ± 148.1)	2090.3 (2094.6 ± 138.5)	1.1 ± 0.4	26.5 (27.8 ± 9.3)
After meals	184.9 (187.5 ± 33.55)	1806.6 (1814.6 ± 183.3)	2044.0 (2056.1 ± 230.9)	2.6 ± 1.1	26.9 (28.3 ± 9.5)

n = 14; Geometric mean (arithmetic mean ± SD), t_{max}: Arithmetic mean ± SD,
$t_{1/2}$: Terminal elimination half-life

Plasma protein binding

The *in vitro* protein bindings of ^{14}C-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 ^{14}C-labeled teneligliptin 20 mg, the unchanged drug and its metabolites, M1, M2, M3, M4 and M5, were found in plasma. The $AUC_{0-\infty}$ 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 (IC_{50}: 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 ^{14}C-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 P-glycoprotein 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 (IC_{50}: 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*).

Subjects with renal impairment

When subjects with renal impairment were administered a single oral dose of 20 mg of teneligliptin, there was no marked change in C_{max} and $t_{1/2}$ of teneligliptin according to the severity of renal impairment. On the other hand, $AUC_{0-\infty}$ in subjects with mild ($50 \leq Ccr \leq 80$ mL/min), moderate ($30 \leq Ccr < 50$ mL/min) and severe ($Ccr < 30$ mL/min) renal impairment was approximately 1.25 times, 1.68 times and 1.49 times, respectively, compared to that in healthy adults, and AUC_{0-43hr} in subjects with end stage renal failure was approximately 1.16 times compared to that in healthy adults. In addition, 15.6% of the administered teneligliptin dose was eliminated by haemodialysis.

Table: Pharmacokinetic parameters of teneligliptin after single oral administration in subjects with renal impairment

Severity of renal impairment	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	$t_{1/2}$ (hr)
Healthy adults, n = 8	178.93 (176.50 ± 38.42)	1748.39 (1772.7 ± 657.3)	25.64 (26.1 ± 5.0)
Mild, n = 8	193.15 (207.96 ± 53.31)	2178.90 (2234.2 ± 278.6)	25.60 (27.7 ± 7.9)
Ratio to healthy adults (%) [90% confidence interval]	107.95 [86.24-135.12]	124.62 [100.97-153.82]	99.84 [75.94-131.27]
Moderate, n = 8	199.55 (203.63 ± 42.33)	2930.17 (3090.3 ± 868.6)	34.93 (36.0 ± 11.0)
Ratio to healthy adults (%) [90% confidence interval]	111.53 [89.10-139.60]	167.59 [135.78-206.86]	136.19 [103.59-179.06]
Severe, n = 8	186.39 (191.63 ± 49.07)	2603.17 (2833.3 ± 652.3)	26.26 (29.8 ± 11.0)
Ratio to healthy adults (%) [90% confidence interval]	104.17 [82.10-132.18]	148.89 [119.10-186.13]	102.41 [76.61-136.89]

Severity of renal impairment	C_{max} (ng/mL)	AUC_{0-43hr} (ng·hr/mL)	$t_{1/2}$ (hr)
Healthy adults, n = 8	192.69 (195.75 ± 43.28)	1568.38 (1569.5 ± 345.5)	17.41 (18.3 ± 5.7)
Subjects with end stage renal failure, n = 8	211.26 (219.00 ± 118.91)	1826.06 (1820.9 ± 285.4)	22.85 (23.6 ± 5.8)
Ratio to healthy adults (%) [90% confidence interval]	109.64 [82.30-146.06]	116.43 [98.10-138.19]	131.20 [98.26-175.18]

Geometric least square mean (arithmetic mean ± SD)
Healthy adults, Ccr>80 mL/min; mild, 50≤Ccr≤80 mL/min; moderate, 30≤Ccr<50 mL/min; severe, Ccr<30 mL/min.
$t_{1/2}$: Terminal elimination half-life

Subjects with hepatic impairment

When subjects with hepatic impairment were administered a single oral dose of 20 mg of teneligliptin, C_{max} of teneligliptin in subjects with mild (total score of 5 to 6 on the Child-Pugh Classification) and moderate (total score of 7 to 9 on the Child-Pugh Classification) hepatic impairment was approximately 1.25 times and 1.38 times, respectively, compared to that in healthy adults, and $AUC_{0-\infty}$ was approximately 1.46 times and 1.59 times, respectively. There has been no clinical experience in subjects with severe hepatic impairment (total score of >9 on the Child-Pugh Classification).

Table: Pharmacokinetic parameters of teneligliptin after single oral administration in subjects with hepatic impairment

Severity of hepatic impairment	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	$t_{1/2}$ (hr)
Healthy adults, n = 8	200.58 (185.88 ± 84.65)	1610.10 (1548.8 ± 209.1)	21.95 (24.8 ± 6.4)
Mild, n = 8	251.64 (229.25 ± 86.16)	2348.28 (2207.9 ± 790.0)	26.69 (27.9 ± 7.1)
Ratio to healthy adults (%) [90% confidence interval]	125.45 [97.07-162.14]	145.85 [122.13-174.17]	121.56 [94.13-156.99]
Moderate, n = 8	276.24 (247.63 ± 112.95)	2566.69 (2418.9 ± 505.8)	30.21 (30.9 ± 6.6)
Ratio to healthy adults (%) [90% confidence interval]	137.72 [106.56-177.99]	159.41 [133.49-190.37]	137.59 [106.54-177.68]

Geometric least square mean (arithmetic mean ± SD)
Mild, total score of 5 to 6 on the Child-Pugh Classification; moderate, total score of 7 to 9 on the Child-Pugh Classification.
$t_{1/2}$: Terminal elimination half-life

Pharmacokinetics in the elderly

When healthy elderly subjects (aged ≥65 years and ≤75 years, n = 12) and non-elderly subjects (aged ≥45 years and <65 years, n = 12) were administered a single oral dose of 20 mg of teneligliptin under fasting condition, the ratio of geometric least square means (90% confidence interval) of C_{max}, $AUC_{0-\infty}$ and $t_{1/2}$ in elderly subjects to those in non-elderly subjects was 1.006 (0.871-1.163), 1.090 (0.975-1.218) and 1.054 (0.911-1.219), and the parameters of teneligliptin were similar in elderly and non-elderly subjects.

Drug interactions

1) Coadministration with ketoconazole
The influence of concomitant administration of ketoconazole on the pharmacokinetics of teneligliptin is shown in the following table.

Table: Effects of concomitant ketoconazole on the pharmacokinetics of teneligliptin

Concomitant drug	Concomitant drug Dose	Teneligliptin Dose	Pharmacokinetic parameter of teneligliptin, Ratio of geometric mean [90% confidence interval] Combination/single	
			C_{max}	$AUC_{0-\infty}$
Ketoconazole	400 mg	20 mg	1.37 [1.25 - 1.50]	1.49 [1.39 - 1.60]

2) Coadministration with other antidiabetic drugs
When teneligliptin was concomitantly administered with canagliflozin, pioglitazone, glimepiride or metformin, no obvious effect of concomitant administration on the pharmacokinetics of teneligliptin and these drugs was observed.

Effects on electrocardiogram

When healthy adults were administered a repeated oral dose of 40 mg or 160 mg of teneligliptin once daily for 4 days, a maximum mean (and upper limit of 90% confidence interval) of changes in QTcI

(individually corrected QTc) interval corrected for placebo was 3.9 (7.6) msec in the 40 mg group 3 hours after the completion of administration and 9.3 (13.0) msec in the 160 mg group 1.5 hours after the completion of administration (see section 4.4 and 4.9). [The usual approved dosage of this product is 20 mg of teneligliptin once daily, and the maximum dosage is 40 mg once daily (see section 4.2).]

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. $AUC_{0\text{-}24hr}$ 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. $AUC_{0\text{-}24hr}$ 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

D-Mannitol, corn starch, hydroxypropylcellulose, anhydrous silicic acid, magnesium stearate, hypromellose, macrogol 400, titanium oxide, red ferric oxide, hydrogenated oil

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

42 months

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

The products are packed into polyvinylchloride film / aluminum foil blister sheets of 10 tablets. 3 blister sheets or 10 blister sheets are packaged in aluminum bags and then in carton box. Carton contains 30 or 100 tablets.

6.6 Special precautions for disposal

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

7. MARKET AUTHORIZATION HOLDER

Mitsubishi Tanabe Pharma (Thailand) Co., Ltd.
Bangkok, Thailand

Manufactured by:

Mitsubishi Tanabe Pharma Factory Ltd.
Yoshitomi Plant, Fukuoka, Japan

Packaged and released by:

PT Mitsubishi Tanabe Pharma Indonesia
Bandung, Indonesia.

8. MARKETING AUTHORIZATION NUMBERS

1C 15074/63 (NC)

9. DATE OF AUTHORIZATION

7 Apr 2020

10. DATE OF REVISION OF THE TEXT[1]

[1] September 2021