TN44451

TENELIGLIPTIN

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GLIPTEN®
20mg Film-Coated Tablet
ORAL HYPOGLYCEMIC AGENT

FORMULATION
Each film-coated tablet contains:
Teneligliptin hydrobromide hydrate equivalent to Teneligliptin 20mg

DESCRIPTION
Yellow colored, circular biconvex film-coated tablets plain on both sides.

PHARMACOLOGICAL PROPERTIES
PHARMACODYNAMICS
Mechanism of action
Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are secreted from the gastrointestinal tract in response to a meal. Incretin hormones regulate plasma glucose levels by stimulating glucose-dependent insulin release from pancreatic beta cells and inhibiting glucagon secretion from pancreatic alpha cells. The enzyme Dipeptidyl Peptidase IV (DPP-4) however, rapidly degrades both GLP-1 and GIP within a few minutes. Teneligliptin exerts its hypoglycemic action by suppressing the degradation of GLP-1 via inhibition of dipeptidyl peptidase-4 (DPP-4) enzymes thereby increasing blood concentrations of active GLP-1. Teneligliptin inhibits human plasma DPP-4 activity in a concentration-dependent manner with an in vitro IC50 value (95% confidence interval) of 1.75 (1.62-1.89) nmol / L.

In subjects with Type 2 diabetes, Teneligliptin 20mg once daily inhibits DPP-4 activity by 89.7% 2 hours after oral administration and by 61.8% 24-hours post dose. Teneligliptin 20mg once daily in the morning significantly increases plasma GLP-1 and significantly decreases plasma glucagon levels after breakfast, lunch and dinner. Once daily morning administration of Teneligliptin 20 mg improves fasting blood glucose levels and 2 hr post prandial blood glucose levels after each meal (breakfast, lunch and dinner).

PHARMACOKINETICS
Teneligliptin is rapidly absorbed. Peak Teneligliptin plasma concentrations (T_{max}) occur 1.8 hrs and 1 hr after single oral administration of a 20mg and 40mg dose, respectively. Plasma AUC_{0-inf} of Teneligliptin increases in a dose proportional manner; following single oral 20 mg and 40 mg dose in healthy volunteers, mean plasma AUC_{0-inf} of Teneligliptin was 2,028.9 ng.hr/ml and 3,705.1 ng.hr/ml, C_{max} was 187.2 ng/ml and 382.4 ng/ml, and apparent terminal half-life ($t_{1/2}$) was 24.2 and 20.8 hrs, respectively (See Table 1).

Table 1. Pharmacokinetic parameters of a single oral dose of Teneligliptin in healthy adults.

Dose	C_{max} (ng / mL)	AUC_{0-inf} (ng.hr / mL)	T_{max} (hr)	$t_{½}$ (hr)
20mg	187.20 ± 44.70	2,028.9 ± 459.5	1.8 (1.0-2.0)	24.2 ± 5.0
40mg	382.40 ± 89.83	3,705.1 ± 787.0	1.0 (0.5-3.0)	20.8 ± 3.2

n = 6, mean ± standard deviation T_{max}: median (minimum – maximum)

Plasma C_{max}, AUC_{0-inf} of Teneligliptin increases at steady-state compared to the first dose (See Table 2).

Table 2. Pharmacokinetic parameters of repeated oral administration of Teneligliptin in healthy adults.

	C_{max} (ng / mL)	AUC_{0-24hr} (ng.hr / mL)	AUC_{0-inf} (ng.hr / mL)	T_{max} (hr)	$t_{½}$ (hr)
After the first dose	160.60 ± 47.26	1,057.2 ± 283.9	1,627.9 ± 427.8	1.0 (0.4-2.0)	25.8 ± 4.9
7 days after the administration	220.14 ± 59.86	1,514.6 ± 370.5	2,641.4 ± 594.7	1.0 (1.0-1.0	30.2 ± 6.9

n = 7, mean ± standard deviation T_{max}: median (minimum – maximum)

Coadministration of Teneligliptin with food reduces C_{max} by 20%, increases T_{max} from 1.1 to 2.6 hours but does not affect AUC_{inf} of Teneligliptin compared with coadministration without food (fasting state). This change is not clinically meaningful. Teneligliptin can be taken before or after a meal, however administration 1 hour before a meal is preferable (See Table 3). The plasma protein binding rate is 77.6 – 82.2%.

Table 3. Pharmacokinetic parameters of Teneligliptin administered before and after meals in healthy adults.

	C_{max} (ng / mL)	AUC_{0-24hr} (ng.hr / mL)	AUC_{0-inf} (ng.hr / mL)	T_{max} (hr)	$t_{½}$ (hr)
Fasting	232.2 (236.2 ± 43.77)	1,855.5 (1,861.1 ± 148.1)	2,090.3 (2094.6 ± 138.5)	1.1 ± 0.4	26.5 (27.8 ± 9.3)
After a meal	184.9 (187.5 ± 33.55)	1,806.6 (1,814.6 ± 183.3)	2,044.0 (2,056.1 ± 230.9)	2.6 ± 1.1	26.9 (28.3 ± 9.5)

n = 14, geometric mean (arithmetic mean ± standard deviation) T_{max}: arithmetic mean ± standard deviation

Metabolism
After a single oral dose of [14C]-labeled Teneligliptin 20mg, 5 metabolites, M1, M2, M3, M4, and M5, are observed in plasma.
In-vitro studies indicate that CYP3A4 and flavin-containing monooxygenase 3 (FMO3) are the major and CYP2D6 and flavin-containing monooxygenase 1 (FMO1) are the minor enzymes responsible for the metabolism of Teneligliptin. In addition, Teneligliptin is a weak inhibitor of CYP2D6, CYP3A4, and FMO; IC50 values: 489.4,197.5 and 467.2 µmol/L, respectively. In vitro Teneligliptin does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C8 / 9, CYP2C19, and CYP2E1. Teneligliptin does not induce CYP1A2 and CYP3A4.

Excretion
Two hundred and sixteen (216) hours after a single 20 mg oral dose of [14C] Teneligliptin, 45.4% of the administered radioactivity was excreted in urine and 46.5% in feces. Approximately 21.5% of an oral dose of Teneligliptin is excreted unchanged in the urine. The renal clearance rate for Teneligliptin is 37-39 mL/hr/kg. The cumulative urinary excretion rates 120 hrs post dose for un-metabolized, M1, M2, and M3 were 14.8%, 17.7%, 1.4% and 1.9% respectively while the cumulative fecal excretion rates 120 hrs post dose for un-metabolized, M1, M3, M4 and M5 were 26.1%, 4.0%, 1.6%, 0.3% and 1.3% respectively.

Renal Impairment
Compared with healthy adult subjects, C_{max} and $t_{½}$ are not significantly changed in subjects with mild (50≤CrCl≤80 mL/min), moderate (30≤CrCl<50 mL/min), or severe (CrCl<30 mL/min) renal impairment (See Table 4). AUC_{0-inf} significantly increases 1.25-fold, 1.68-fold, and 1.49-fold in subjects with mild, moderate, and severe renal impairment, respectively, relative to healthy adult subjects. Compared with healthy adult subjects, C_{max} and $t_{½}$ are not significantly changed in subjects with end stage failure but AUC_{last} increases 1.16-fold (See Table 5). Renal impairment does not have a clinically meaningful effect on the pharmacokinetics of Teneligliptin, dose adjustments are not required in subjects with any degree of renal impairment.

Table 4. Pharmacokinetic parameters of Teneligliptin in subjects with renal impairment.

Degree of Renal Impairment	C_{max} (ng / mL)	AUC_{0-inf} (ng.hr / mL)	$t_{½}$ (hr)
Healthy adult n = 8	178.93 (176.50 ± 38.42)	1,748.39 (1,772.7 ± 657.3)	25.64 (26.1 ± 5.0)
Mild n = 8	193.15 (207.96 ± 53.31)	2,178.90 (2,234.2 ± 278.6)	25.60 (27.7 ± 7.9)
Ratio with 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)	2,930.17 (3,090.3 ± 868.6)	34.93 (36.0 ± 11.0)
Ratio with 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)	2,603.17 (2,833.3 ± 652.3)	26.26 (29.8 ± 11.0)
Ratio with healthy adults (%) [90% confidence interval]	104.17 [82.10-132.18]	148.89 [119.10-186.13]	102.41 [76.61-136.89]

Table 5. Pharmacokinetic parameters of Teneligliptin in subjects with end stage renal disease.

Degree of Renal Impairment	C_{max} (ng / mL)	AUC_{0-43} (ng.hr / mL)	$t_{½}$ (hr)
Healthy adult n = 8	192.69 (195.75 ± 43.28)	1,568.38 (1,569 ± 345.5)	17.41 (18.3 ± 5.7)
End Stage Renal Disease n = 8	211.26 (219 ± 118.91)	1,826.06 (1,820.9 ± 285.4)	22.85 (23.6 ± 5.8)
Ratio with healthy adults (%) [90% confidence interval]	109.64 [82.30-146.06]	116.43 [98.10-138.19]	131.20 [98.26-175.18]

Hepatic Impairment
Compared with healthy adult subjects, C_{max} and $t_{½}$ are not significantly increased in subjects with mild (Child–Pugh Score 5–6) and moderate hepatic impairment (Child–Pugh Score 7–9), See Table 5. AUC_{last} is however increased 1.46-fold and 1.59-fold in subjects with mild and moderate hepatic impairment, respectively. Mild to moderate hepatic impairment does not have a clinically meaningful effect on the pharmacokinetics of Teneligliptin, dose adjustments are not required in subjects with mild to moderate hepatic impairment. There is no clinical experience with Teneligliptin in patients with severe hepatic impairment (Child–Pugh Score > 9).

Table 6. Pharmacokinetic parameters of Teneligliptin in subjects with hepatic impairment.

Degree of liver function disorder	C_{max} (ng / mL)	AUC_{0-inf} (ng. hr / mL)	$t_{½}$ (hr)
Healthy adult n = 8	200.58 (185.88 ± 84.65)	1,610.10 (1,548.8 ± 209.1)	21.95 (24.8 ± 6.4)
Mild n = 8	251.64 (229.25 ± 86.16)	2,348.28 (2,207.9 ± 790.0)	26.69 (27.9 7.1)
Ratio with 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)	2,566.69 (2,418.9 505.8)	30.21 (30.9 ± 6.6)
Ratio with healthy adults (%) [90% confidence interval]	**137.72** [106.56-177.99]	**159.41** [133.49-190.37]	**137.59** [106.54-177.68]

Elderly
The pharmacokinetics of Teneligliptin in healthy elderly subjects (>65 years of age) is not significantly different compared to healthy non-elderly subjects (age < 65 years of age); geometric least mean square ratio (elderly: non-elderly) of C_{max}, AUC_{last}, and t 1/2 are 1.006 (0.871-1.163), 1.090 (0.975-1.218) and 1.054 (0.911-1.219), respectively. No dosage adjustment is required in elderly subjects.

INDICATIONS
Teneligliptin is indicated for the treatment of type 2 diabetes mellitus as monotherapy or in combination with other oral hypoglycemic agents (e.g., metformin, pioglitazone, sulfonylureas, glinides, and α glucosidase inhibitors) and insulin.

CONTRAINDICATIONS
Teneligliptin is contraindicated in the following:
- Any patient with 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).

DOSAGE AND ADMINISTRATION
Recommended dose is 20mg, taken orally once a day in adults. If the effect is insufficient, the dose can be increased to 40mg once a day. Or as prescribed by the physician.

PRECAUTIONS
- Patients with severe hepatic impairment (Safety has not been investigated/established).
- Patients with heart failure NYHA classification III-IV (Safety has not been investigated/established).
- Patients with pituitary or adrenal insufficiency, poor nutritional state, starvation, irregular food intake, or debilitating condition, intensive exercise or excessive alcohol intake (may enhance blood glucose lowering effect).
- Patients taking medication that may enhance the blood glucose lowering effect of Teneligliptin (β-blockers, MAO Inhibitors, etc.) or attenuate the blood glucose lowering effect of Teneligliptin (steroids, thyroid hormones, etc.)
- History of bowel obstruction or a history of abdominal surgery. (Rare cases of intestinal obstruction have been reported with the use of DDP-4 Inhibitors, including Teneligliptin).
- Patients taking sulfonylureas or insulin (The risk of hypoglycemia is increased). Reduce dose of sulfonylurea or insulin.
- In a randomized, double-blind, placebo and moxifloxacin-controlled thorough QT/QTc comparative study (n=240), supratherapeutic doses of Teneligliptin 160mg once daily (8 times the usual dose and 4 times the maximum recommended daily dose) momentarily prolonged QTc interval by 9.3 msec at around the time of T_{max}. No clinically significant change in QTc interval was observed with the maximum recommended dose of Teneligliptin 40mg once daily (3.9 msec). In clinical trials involving up to 904 subjects with Type 2 diabetes, no adverse events related to QTc prolongation were detected with Teneligliptin when used up to its maximum daily dose of 40 mg/day. Nevertheless, Teneligliptin should be used with caution in subjects who are prone to QT prolongation; patients with or with a medical history of arrhythmia, bradycardia, heart failure, low serum potassium, Torsades de pointes, or patients using antiarrhythmic drugs (Class IA and III antiarrhythmics).

USE IN 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).

ADVERSE EFFECTS
Hypoglycemia
In clinical trials using Teneligliptin as monotherapy, the incidence of hypoglycemia was 1.1%. The incidence of hypoglycemia when Teneligliptin was used in combination with metformin, pioglitazone, and α-glucosidase inhibitors was 1.1%, 1.5%, and 1.3%, respectively, and not significantly different from incidence rates in placebo treated subjects. Hypoglycemic episodes were of mild intensity, not dose related, and did not cause any subjects to discontinue treatment. The incidence of hypoglycemia is increased when Teneligliptin is added to treatment with a glinide (3.8%) and a sulfonylurea (8.9%). Serious hypoglycemic symptoms with or without loss of consciousness have been reported when DPP-4 inhibitors are combined with sulfonylureas. Therefore, when Teneligliptin is used in combination with sulfonylurea, the dose of the sulfonylurea should be reduced

Table 7 Other Adverse Reactions

Adverse Reaction	Frequency ≤ 1%
Gastrointestinal Disorders	Intestinal Obstruction*, Constipation, abdominal bloating, abdominal discomfort, nausea, abdominal pain, flatulence stomatitis, gastric polyps, colon polyps, duodenal ulcer, reflux esophagitis, diarrhea, loss of appetite, increased amylase, increased lipase, acute pancreatitis
Investigations	Elevated AST, ALT, γ-GTP and ALP
Kidney, Urinary system	Proteinuria, urine ketone-positive, hematuria
Skin & Subcutaneous Tissue Disorders	Eczema, rash, itching, allergic dermatitis, phemphigus**
Respiratory System	Interstitial pneumonia
Other	Elevated CPK, serum potassium, uric acid. Malaise, Allergic rhinitis.

* Rare cases of intestinal obstruction have been reported with the use of DDP-4 Inhibitors, including Teneligliptin. Caution should be used in patients with a history of abdominal surgery or intestinal obstruction. If abdominal pain, severe constipation, abdominal distention or vomiting persists, Teneligliptin should be discontinued and appropriate measures should be taken.
** If blisters, erosions etc. on the skin are observed, take appropriate measures and discontinue administration of Teneligliptin.
*** Rare cases of interstitial pneumonia have been reported with the use of DDP-4 Inhibitors, including Teneligliptin.
Administration of Teneligliptin should be discontinued if interstitial pneumonia (with symptoms of cough, dyspnea, fever, pulmonary sound abnormalities) is suspected; appropriate measures (promptly examine chest X-ray, chest CT, serum marker) including administration of corticosteroids should be taken.

DRUG INTERACTIONS
CYP3A4 and flavin monooxygenase 3 (FMO3) are the major and CYP2D6 and flavin monooxygenase 1 (FMO1) are the minor hepatic enzymes responsible for the metabolism of Teneligliptin. Teneligliptin is a weak inhibitor of CYP2D6, CYP3A4, and FMP (IC50 values; 489.4, 197.5, and 467.2 μmol/L, respectively) but shows no inhibitory effect on CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C8/9, CYP2C19, and CYP2E1. Teneligliptin does not induce CYP3A4 or CYP1A2.

Ketoconazole (400mg) a potent inhibitor of CYP3A4 increased C_{max} and AUC of Teneligliptin by 1.37-fold and 1.49-fold, respectively which was less than 2-fold and not considered clinically significant (See Tables 6 and 7). The half-life ($t_{1/2}$) of Teneligliptin was unchanged with ketoconazole coadministration. The combination of Teneligliptin with drugs and food that inhibit CYP3A4 are not expected to cause marked, clinically significant increases in the exposure to Teneligliptin. No dose adjustments are required.

The pharmacokinetics of Teneligliptin is not significantly affected by coadministration with pioglitazone or metformin. Teneligliptin does increase the exposure to metformin by a non-clinically relevant 20.5% (See Tables 6 and 7). No dosage adjustment is needed when Teneligliptin is combined with either pioglitazone or metformin.

When coadministered, neither Teneligliptin nor glimepiride affect each other's pharmacokinetic profile in any clinically meaningful way (See Tables 6 and 7). The risk of hypoglycemia may be increased when Teneligliptin is used concomitantly with insulin and insulin secretagogues such as sulfonylureas and glinides. The dosage of insulin or the insulin secretagogue should be adjusted.

Table 6 Effect of Coadministered Medications on Systemic Exposure of Teneligliptin

Coadministered Drug	Coadministered Drug Dose	Teneligliptin Dose	Geometric LS Mean Ratio (With/Without Coadministered Drug) [90% Confidence Interval]	
			AUC_{0-inf}	C_{max}
Ketoconazole	400mg OD	20mg OD	1.37 (1.25-1.50)	1.49 (1.39-1.60)
Metformin	850mg BID	40mg OD	1.042 (0.997-1.089)	0.907 (0.853-0.965)
Glimepiride	1mg OD	40mg OD	0.926 (0.894-0.859)	0.971 (0.866-1.088)
Pioglitazone	30mg OD	40mg OD	1.005 (0.957-1.045)	1.117 (0.984-1.266)

OD = Once daily, BID = Twice daily

Table 7 Effect of Teneligliptin on Systemic Exposure of Coadministered Drugs

Coadministered Drug	Coadministered Drug Dose	Teneligliptin Dose	Geometric LS Mean Ratio (With/Without Coadministered Drug) [90% Confidence Interval]	
			AUC_{0-inf}	C_{max}
Metformin	850mg BID	40mg OD	1.209 (1.143-1.278)	0.907 (0.853-0.965)
Glimepiride	1mg OD	40mg OD	1.023 (0.978-1.071)	0.971 (0.866-1.088)
Pioglitazone	30mg OD	40mg OD	1.134 [1.060-1.213]	1.004 [0.917-1.100]
M-III			1.116 [1.056-1.180]	1.041 [0.957-1.113]
M-IV			1.088 [1.032-1.147]	1.028 [0.963-1.096]

OD = Once daily, BID = Twice daily

OVERDOSAGE
In the event of overdose, 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 if required.

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without a prescription.

STORE AT TEMPERATURES BELOW 30°C.

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AVAILABILITY
Alu-alu blister x 10's (Box of 30's)
FOR SUSPECTED ADVERSE DRUG REACTION, REPORT TO THE FDA: www.fda.gov.ph *Seek medical attention immediately at the first sign of any adverse drug reaction.*
Registration No.: DR-XY45743

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