

Front side
Paper: 35 - 45 gsm

Size: 260 (L) x 420 (H) mm
Folding size: 35 x 140 mm
Drg. No. : 9921442-002
Carton size: 46 x 28 x 106 mm

260 mm

120 mm

140 mm



TENELIGLIPTIN

TENEPRIDE-20

20 mg Film Coated Tablet

Antidiabetic agent (Dipeptidyl peptidase 4 (DPP-4) inhibitors)

PRODUCT NAME:
Tenepride-20

DOSAGE FORM AND STRENGTH:
Film coated tablets 20 mg

PHARMACOLOGIC CATEGORY:
Antidiabetic agent (Dipeptidyl peptidase 4 (DPP-4) inhibitors)

PRODUCT DESCRIPTION
Pink coloured, circular, biconvex film coated tablets

FORMULATION/COMPOSITION:
Each film-coated tablet contains:
Teneligliptin Hydro bromide Hydrate
equivalent to Teneligliptin 20 mg

PHARMACODYNAMICS/PHARMACOKINETICS:

Pharmacodynamics:

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

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

- 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.
- 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.

Pharmacokinetics:

Plasma concentrations

- 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.

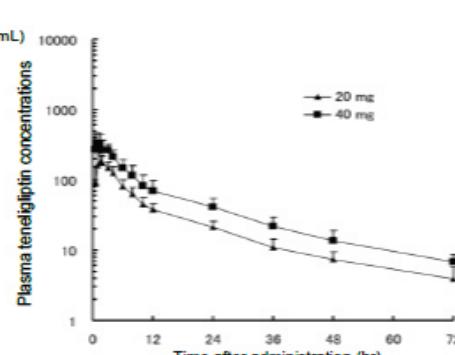


Figure: Plasma concentration-time profiles of Teneligliptin after single oral administration in healthy adults (mean ± SD; n = 6)

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

	C _{max} (ng/mL)	AUC _{0-∞} (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

- 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 _{0-24 hr} (ng·hr/mL)	AUC _{0-∞} (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

- 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 _{0-7 hr} (ng·hr/mL)	AUC _{0-∞} (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 14C-labeled teneligliptin (20, 100 and 500 ng/mL) to human plasma were 77.6% to 82.2%.

Metabolism

- 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 AUC_{0-∞} 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%, 0.3% and 1.1%, respectively.
- 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

- 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.
- 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.
- 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 (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*).

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-∞} in subjects with mild (50 ≤ Cr ≤ 80 mL/min), moderate (30 ≤ Cr < 50 mL/min) and severe (Cr < 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_{0-43 hr} 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 hemodialysis.

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

Severity of renal impairment	C _{max} (ng/mL)	AUC _{0-∞} (ng·hr/mL)	t _{1/2} (hr)
Healthy adults, n = 8	178.93 (176.50 ± 38.42)	1748.39 (1722.7 ± 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 _{0-43 hr} (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, Cr > 80 mL/min; mild, 50 ≤ Cr ≤ 80 mL/min; moderate, 30 ≤ Cr < 50 mL/min; severe, Cr < 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-∞} 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-∞} (ng·hr/mL)	t _{1/2} (hr)
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DOSAGE AND MODEL ROUTE OF ADMINISTRATION:

The usual adult dosage is 20 mg of Teneliglitin administered orally once daily. If efficacy is insufficient, the dose may be increased to 40 mg once daily with close monitoring of clinical course.

CONTRAINDICATIONS & PRECAUTION(S), WARNING(S):

Teneliglitin is contraindicated in the following patients.

- Patients with a history of hypersensitivity to any of the ingredients of this product
- 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 hyperglycemia with transfusion and insulin.]
- 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.]

PRECAUTIONS & WARNINGS:

Careful Administration

Teneliglitin 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

- 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.

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).

Other Precautions

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 Teneliglitin once daily, and the maximum dosage is 40 mg once daily.]

PREGNANCY AND LACTATION:

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.]

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.]

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%.

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. 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 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.

ADVERSE EFFECTS:

Clinically significant adverse drug reactions

- 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.
- 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.
- 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.
- Interstitial pneumonia (incidence unknown): Interstitial pneumonia may occur. If any abnormalities, such as cough, dyspnoea, pyrexia and lung creptitation, 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.
- 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.
- 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.

Type/Frequency	≥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

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



OVERDOSAGE AND TREATMENT:

The maximum doses of Teneliglitin 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 Teneliglitin at the 2 doses.

QT interval prolongation has been reported after administration of this product at a dose of 160 mg once daily.

STORAGE CONDITION:

STORE AT TEMPERATURES NOT EXCEEDING 30°C.

DOSAGE FORMS AND PACKAGING AVAILABLE:

Film coated tablets

Alu-Alu Blister Pack of 10's (Box of 30's)

INSTRUCTIONS AND SPECIAL PRECAUTIONS FOR HANDLING AND DISPOSAL (IF APPLICABLE):

Not Applicable

NAME AND ADDRESS OF MARKETING AUTHORIZATION HOLDER:

Marketing Authorization Holder

Brown & Burk Philippines Inc
U-501, 5/F, SEDCCO 1 Bldg., 120 Rada cor., Legaspi Sts., Legaspi Village, Makati City, Philippines

NAME AND ADDRESS OF MANUFACTURER:

MICRO LABS LIMITED

92, Sipcot Industrial Complex,

Hosur – 635 126, India

CAUTION STATEMENT:

FOODS, DRUGS, DEVICES, AND COSMETICS ACT PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

ADR REPORTING STATEMENT:

FOR SUSPECTED ADVERSE DRUG REACTION, REPORT TO THE FDA: www.fda.gov.ph

Seek medical attention immediately at the first sign of Adverse Drug Reaction.

REGISTRATION NUMBER:

DR-XY48005

DATE OF FIRST AUTHORIZATION:

06 MAY 2022

DATE OF REVISION OF PACKAGE INSERT:

July 2022

EXG-ML01I-1811

PHARMACODE READING DIRECTION



PHARMACODE READING DIRECTION

311

MICRO LABS LIMITED, BANGALORE, INDIA					
1	Product Name	Tenepride-20			<u>Colours Used</u>
2	Strength	20 mg			<input checked="" type="checkbox"/> BLACK
3	Component	Leaflet			
4	Category	Export - Philippines			
5	Dimension	260 (L) x 420 (H) mm			
6	Artwork Code	EXG-ML01I-1811			
7	Pharma Code	311			
8	Reason for Change	New Artwork			
		Prepared by (DTP)	Checked by (PD)	Approved by	
Sign	Date			Head CQA	Head Production/ Packing (Site)
Sign	Kanthalraju L.				
Date	10-11-2022				