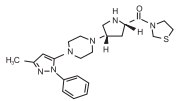
Tenliptin 20mg Tablets

(Teneligliptin) Tablets

COMPOSITION
Each film coated tablet contains:
Teneligliptin 20mg
(As Teneligliptin Hydrobromide Hydrate).
As per Innovator's Specifications.

DESCRIPTION
Teneligliptin is a DPP-4 inhibitor for treatment of type 2 diabetes mellitus (T2DM). It has the molecular formula $C_{22}H_{30}N_8OS.2H^2Br\ xH_2O$. Its structural formula is as follows:



CLINICAL PHARMACOLOGY
Mechanism of Action
The glucagon-like peptide-1 (GLP-1) is secreted from alimentary canal in response to meal that promotes insulin secretion from pancreas and regulates blood sugar post meal by controlling glucagon secretion. Teneligliptin exhibits a hypoglycemic effect by controlling the decomposition of GLP-1 by inhibiting dipeptidyl peptidase-4 (DPP-4) activity and thereby increasing blood concentration of active GLP-1.

PHARMACOKINETICS
Plasma concentration:
(1) Single-dose administration: The plasma concentration changes and the pharmacokinetic parameters of teneligliptin after a single oral dose of 20mg and 40mg of teneligliptin given empty stomach to the healthy adults are shown below.

Strengths	C_{max} (ng/mL)	AUC $_{0\text{-}inf}$ (ng.hr/mL)	t_{max} (hr)	$T_{1/2}$ (hr)
20mg	187.20 ± 44.70	2028.9 ± 459.5	1.8 (1.0 - 2.0)	24.2 ± 5.0
40mg	382.40 ± 89.83	3705.0 ± 787.0	1.0 (0.5 - 3.0)	20.8 ± 3.2

(2) Repeated dose administration: The pharmacokinetic parameters of teneligliptin after a repeated dose of 20mg of teneligliptin once daily for seven days given 30 minutes before breakfast to the healthy adults are shown below.

	Cmax (ng/mL)	AUC $_{0.24\ hr}$ (ng.hr/mL)	AUC $_{0\text{-}inf}$ (ng.hr/mL)	tmax (hr)	$t_{1/2}$ (hr)
After 1st. dose	160.60 ± 47.26	1057.2 ± 283.9	1627.9 ± 427.8	1.0 (0.4 - 2.0)	25.8 ± 4.9
7 days after administration	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 Value ± SD
tmax = central value (minimum value - maximum value)

(3) Food effect: Cmax decreased after a single dose of 20mg of teneligliptin given post meal to the healthy adults as compared to empty stomach and t_{max} prolonged from 1.1 hr to 2.6 hr; however, no difference observed in AUC.
Metabolism:
Following a single oral administration of 20mg teneligliptin to the healthy adults, the unaltered substance and the metabolites M1, M2, M3, M4, and M5 were observed in the blood plasma. Mainly, CYP3A4 and Flavin-containing monooxygenases (FMO1 and FMO3) participate in the metabolism of teneligliptin. Teneligliptin showed a weak inhibitory action towards CYP2D6, CYP3A4, and FMO
Excretion:
1) When a single oral dose of 20mg and 40mg teneligliptin was given to the healthy adults on empty stomach, about 21.0 to 22.1% of dose was excreted as unaltered substance in urine, and the renal clearance was 37 to 39mL/hr/kg.
2) When a single oral dose of 20mg teneligliptin was given to the healthy adults, 45.4% of dosage radioactivity was excreted in urine and 46.5% was excreted in feces up to 216 hours after administration.
3) Teneligliptin is a substrate of P-glycoprotein that inhibited the transportation of digoxin up to 42.5% through P-glycoprotein in the concentration of 99μmol/L. Furthermore, teneligliptin showed a weak inhibitory action towards the organic anion transporter OAT 3 appeared in kidney however, it did not show inhibitory action towards OAT 1 and organic cation transporter OCT2 (in vitro).

THERAPEUTIC INDICATIONS
In patients having type 2 diabetes mellitus, the administration of 20mg teneligliptin once daily improved the blood sugar after breakfast, lunch, and dinner and the fasting blood sugar.

Type 2 Diabetes Mellitus: The drug should be used only in patients who have only not sufficiently responded to either of the following treatments:
(a) Diet and/or exercise therapy alone.
(b) Use of sulphonylureas in addition to the diet and/or exercise therapy.
(c) Use of Thiazolidinediones in addition to the diet and/or exercise therapy.

Teneligliptin is a DPP-4 inhibitor for treatment of type 2 diabetes mellitus (T2DM).

DOSAGE AND ADMINISTRATION
The usual adult dosage is 20mg of teneligliptin administered orally once daily. If efficacy is insufficient, the dose may be increased up to 40mg once daily while closely monitoring the clinical course. Teneligliptin tablets are to be administered orally without regard to meal. Do not crush or chew tablets.

Special Populations:
Pediatric Use: The safety of this product in low birth weight baby, newborn baby, infant, or little child has not been established.
Geriatric Use: In general, elderly patients often have physiological hypofunction; and therefore, teneligliptin should be administered carefully.
Renal impairment: As determined from the pharmacokinetic characteristics of teneligliptin, the extent of increase in the exposure level of teneligliptin in patients with renal impairment will not pose any significant safety risk. Thus, no dose adjustment is proposed in renal impaired patients.
Hepatic impairment: As determined from the pharmacokinetic characteristics of teneligliptin, the extent of increase in the exposure level of teneligliptin in patients with mild to moderate hepatic impairment will not pose any significant safety risk. There was no clinical experience in severe degree hepatic dysfunction patients.

CONTRAINDICATIONS
Teneligliptin Tablets are contraindicated in patients with:
Hypersensitivity to the drug or any of its components.
Severe ketosis, diabetic coma or pre-coma and also for immediate remedy in type

1 diabetes of hyperglycemias with infusion and insulin.
- Patients with severe trauma, before and after surgery and when the blood glucose level is controlled with insulin injection.

WARNING AND PRECAUTIONS

This medicine should be carefully administered in the following patients:

1) Patient with severe hepatic dysfunction.
2) It should not be used in patients with history of acute pancreatitis. In case a patient develops acute pancreatitis the drug should be withdrawn and immediate physician consultation should be done.
3) Patient with heart failure (NYHA class III–IV) (as there is no usage experience and safety has not been established).
4) Co-administration of sulfonylurea medication or insulin formulation (Risk of hypoglycemia may increase). In order to reduce the risk of hypoglycemia caused by sulfonylurea or insulin formulation, consider decreasing the dose of sulfonylurea or insulin formulation when given in combination with teneligliptin.
5) Hypoglycemia may occur in patients with: Adrenal insufficiency, malnutrition, starved state, irregular dietary intake, insufficient dietary intake or hyposthenia, vigorous muscular movement and patient with excessive alcohol consumption. Attention should be paid while administration of this drug to the patients who are engaged in car driving or working at heights.
6) Patient with history of abdominal surgery or intestinal obstruction.
7) QT prolongation may occur in patients having arrhythmia such as severe bradycardia or having its history, patient having heart disease such as congestive heart failure, and patient having hypokalemia. It is desirable to avoid the medication in the patients having QT prolongation or its history (such as hereditary QT prolongation syndrome) or the patients having history of Torsade's de pointes.
8) Consider its application only to the patient diagnosed with Type 2 diabetes mellitus (T2DM). In addition to T2DM, pay attention to diseases having symptoms (such as renal glycosuria, thyroid dysfunction) similar to diabetes, such as abnormal glucose tolerance/positive urine sugar.
9) During administration of this product, regularly check the blood sugar, check the effect of the drug. In case, the drug effect is insufficient even after taking this product for 3 months, then change to other treatment.

ADVERSE REACTIONS

The most commonly reported adverse reactions include hypoglycemia, constipation, feeling of abdomen enlarged, abdominal discomfort, nausea, abdominal pain, meteorism, stomatitis, eczema, rash, pruritus, dermatitis and malaise and others adverse reactions reported with teneligliptin are:
• Cold sweat, hungry feeling, tremor of limbs, abdominal pain [intestinal obstruction] • General malaise, loss of appetite, yellowing of the skin or the whites of the eyes [hepatic function disorder]
• Dry cough, respiratory distress, fever [interstitial pneumonia] • Rash with blister [pemphigoid]

DRUG INTERACTIONS

Drug name and other details	Clinical symptoms and treatment methods	Mechanism and Risk factors
Medicines for diabetic disease: - Drugs for diabetes Sulfonylurea fast-acting insulin secretagogue α-glucosidase inhibitor Biguanide drugs Thiazotidinediones	Since hypoglycemia might occur, these drugs should be administered while carefuly moniting the patient's condition. Particularly, when co-administered with sulfonylurea or insulin formulation, there is a possibility of higher risk of hypoglycemia. In order to reduce the	Hypoglycemic action is increased.
GLP-1 analog preparation SGLT2 inhibitor insulin preparation	risk of hypoglycemia caused by sulfonylurea or insulin formulation, consider decreasing the quantity of sulfonylurea or insulin formulation. When hypoglycemia is observed, usually, cane sugar should be given, and when co-administered with α- glucosidase inhibitor, glucose should be given	
Drugs increasing hypoglycemic action β-blocking agents Salicylic acid drugs Monoamine oxidase inhibitor	Since the blood sugar may further decrease, these drugs should be administered while carefully observing the patient's condition in addition to blood sugar level.	Hypoglycemic action is increased.
Drugs decreasing hypoglycemic action - Adrenaline - Adrenocortical hormone - Thyroid hormone	Since the blood sugar may increase, these drugs should be administered while carefully observing the patient's condition in addition to blood sugar level.	Hypoglycemic action is decreased.
Drugs known to case QT prolongation - Class IA anti arrhythmic drugs: Quinidine sulfate hydrate, procainamide hydrochloride - Class III antiarrhythmic drugs: amiodarone hydrochloride, sotalol hydrochloride	QT prolongation might occur.	QT prolongation is seen with single administration of these drugs.

OVERDOSE

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy if required.

STORAGE

- Store below 30ºC.
- Protect from heat, light and moisture.

PRESENTATION

Teneligliptin (Teneligliptin) 20mg is available as pack of 14's.

To be sold on the prescription of a registered medical practitioner only.

Keep all medicines out of the reach of children.

Manufactured by :
Indus Pharma (Pvt.) Ltd.
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Karachi-74900, Pakistan.

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