TEN20® Tablets

Each Tablet Contains

Teneligliptin – 20 mg

PHARMACEUTICAL INFORMATION –

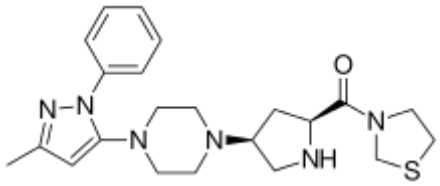
TENELIGLIPTIN

Generic name: **Teneligliptin**

Chemical name: {(2*S*,4*S*)-4-[4-(3-Methyl-1-phenyl-1*H*-pyrazol-5-yl)-1-piperazinyl]-2-pyrrolidinyl}(1,3-thiazolidin-3-yl)methanone

Molecular mass: 426.58 g/mol

Structural formula:



Empirical formula – $C_{22}H_{30}N_6OS$

Storage and Stability:

PHARMACOKINETIC PROPERTIES –

Teneligliptin

After oral administration of a single 20 mg and 40 mg dose to healthy subjects, teneligliptin was rapidly absorbed, with peak plasma concentrations (mean T max) occurring at 1.8 hours and 1 hour post dose. Plasma AUC of teneligliptin increased in a dose-proportional manner. Following a single oral 20 mg and 40 mg dose to healthy volunteers, mean plasma AUC of teneligliptin was 2028.9 and 3705.1 ng*hr/ml, Cmax was 187.2 and 382.4 ng/ml, and apparent terminal half-life (t1/2) was 24.2 and 20.8 hours. Plasma AUC of teneligliptin increased following 20 mg doses at steady-state compared to the first dose. Coadministration with food reduces the Cmax by 20%, increases the Tmax from 1.1 to 2.6 hours but does not affect the AUC of teneligliptin as compared to that in the fasting state. The plasma protein binding rate is 77.6 – 82.2%.

Following a 20 mg single oral dose of [14C] teneligliptin, 5 metabolites M1, M2, M3, M4 and M5 were observed. In vitro studies indicated that CYP3A4 and flavin-containing monooxygenase (FMO1 and FMO3) are involved in the metabolism of teneligliptin. Teneligliptin does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C8/9, CYP2C19, CYP2E1, is a weak inhibitor of CYP2D6, CYP3A4, and FMO (IC50 value : 489.4, 197.5 and 467.2 µmol/l) and does not induce CYP3A4 and CYP1A2.

Following a 20 mg single oral dose of [14C] teneligliptin, 45.4% of administered radioactivity was excreted in urine and 46.5% in faeces till 216 hours after dose. The cumulative urinary excretion rates for upto 120 hours for un-metabolized, M1, M2, and M3 were 14.8%, 17.7%, 1.4% and 1.9% respectively while the cumulative faecal excretion rates for un-metabolized, M1, M3, M4 and M5 were 26.1%, 4.0%, 1.6%, 0.3% and 1.3% respectively.

The single administration of teneligliptin at 20 mg in patients with renal impairment revealed no remarkable changes in Cmax and t1/2 corresponding to the level of renal impair¬ment. Compared with healthy adult subjects, the AUC0–∞ of subjects with mild renal impairment (50 ≤ creatinine clearance [Ccr] ≤ 80 mL/minute), moderate renal impair¬ment (30 ≤ Ccr < 50 mL/minute), and severe renal impair¬ment (Ccr < 30 mL/minute) was approximately 1.25 times, 1.68 times, and 1.49 times higher than that of healthy adult subjects, respectively.

A single administration of teneligliptin 20 mg in patients with hepatic impairment revealed that the Cmax of subjects with mild hepatic impairment (Child–Pugh classification: total score 5–6) and moderate hepatic impairment (Child–Pugh classification: total score 7–9) was approximately 1.25 times and 1.38 times that of healthy adult subjects, respectively. Compared to healthy adult subjects, the AUC0–∞ of subjects with mild and moderate hepatic impairments was approxi¬mately 1.46 times and 1.59 times higher than that of healthy adult subjects, respectively. There have been no previous clinical studies using teneligliptin in patients with severe hepatic impairment (Child–Pugh classification: total score was greater than 9).

PHARMACODYNAMIC PROPERTIES & MECHANISM OF ACTION –

Teneligliptin is a DPP-4 inhibitor, which is believed to exert its actions in patients with type 2 diabetes by slowing the inactivation of incretin hormones. Concentrations of the active intact hormones are increased by teneligliptin, thereby increasing and prolonging the action of these hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. These hormones are rapidly inactivated by the enzyme, DPP-4. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular

signaling pathways involving cyclic AMP. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. By increasing and prolonging active incretin levels, teneligliptin increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner

INDICATION –

Type 2 diabetes mellitus

The drug product should be used only in patients who have not sufficiently responded to either of the following treatments.

(a) Diet and/or exercise therapy alone

(b) Use of sulfonylureas in addition to diet and/or exercise therapy

(c) Use of thiazolidinediones in addition to diet and/or exercise therapy

CONTRAINDICATIONS –

Teneligliptin is contraindicated in the following:

- Any patient with a 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 –

The usual adult dosage is 20 mg of teneligliptin administered orally once daily. If efficacy is insufficient, the dose may be increased up to 40 mg once daily while closely monitoring the clinical course.

ADVERSE EFFECTS –

The most common adverse reactions reported with teneligliptin are hypoglycemia and constipation.

Other adverse reactions reported with teneligliptin are:

Gastrointestinal Disorders: Intestinal obstruction, abdominal bloating, abdominal discomfort, nausea, abdominal pain, flatulence, stomatitis, gastric polyps, colon polyps, duodenal ulcer, reflux esophagitis, diarrhea, loss of appetite, increased amylase, lipase increased, acute pancreatitis.

Kidney and Urinary system: Proteinuria, urine ketone-positive.

Skin and Subcutaneous Tissue Disorders: Eczema, rash, itching, allergic dermatitis.

Investigations: Increase in AST, ALT, γ-GTP and ALP.
Others: Increased CPK, increased serum potassium, fatigue, allergic rhinitis, elevation of serum uric acid

OVERDOSAGE
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 as dictated by the patient's clinical status.

WARNINGS AND PRECAUTIONS
Teneligliptin should be administered carefully in the following:

- Patients with advanced liver failure (safety has not been established),
- Patients with congestive heart failure (NYHA category III-IV) (safety has not been established),
- Patients with pituitary insufficiency or adrenal insufficiency, poor nutritional state, starvation, an irregular dietary intake, or debilitating condition, intense muscle movement or excessive alcohol intake (may cause low blood sugar),
- Patients with history of abdominal surgery or with a history of bowel obstruction (may cause bowel obstruction),
- Patients with arrhythmia, severe bradycardia or its history, patients with heart disease such as congestive heart failure or patients with low serum potassium, congenital prolonged QT syndrome, history of Torsades de pointes or patients using antiarrhythmic drugs (may cause QT prolongation),
- Patients using an insulin secretagogue (e.g., sulfonylurea) (risk of severe hypoglycaemia).

DRUG INTERACTIONS –

Teneligliptin should be used with caution with drugs that can enhance the blood glucose lowering effect (like β blockers, MAO inhibitors, etc.) and attenuate the blood glucose lowering effect (like steroids, thyroid hormones, etc).

On concomitant therapy with ketoconazole, the geometric least squares mean ratio (concomitant therapy/teneligliptin monotherapy) of Cmax and AUC0-t of unchanged plasma teneligliptin with their two-sided 90% CI is 1.37 [1.25, 1.50] and 1.49 [1.38, 1.60], respectively.

Special Populations

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).

Safety and effectiveness of teneligliptin in pediatric patients have not been established.

SHELF-LIFE -

PACKAGING INFORMATION -