For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

AFOGLIP

1. Generic Name

Teneligliptin Tablets IP 20 mg

2. Qualitative and quantitative composition

Each film-coated tablet contains:

Teneligliptin Hydrobromide Hydrate I.P.

Equivalent to Teneligliptin…….20 mg

Colour: Red Oxide of Iron and Titanium Dioxide coated Mica Pearlescent pigment.

The excipients used are Lactose, Talc, Colloidal Silicon Dioxide, Croscarmellose Sodium, Magnesium Stearate, Microcrystalline Cellulose, Hydroxy Propyl Methyl Cellulose, Isopropyl Alcohol, Red Oxide of Iron & Titanium Dioxide coated Mica pearlescent pigment.

3. Dosage form and strength

Dosage form: Film Coated tablet

Strength: 20 mg

4. Clinical particulars

4.1 Therapeutic indication

For the treatment of type 2 Diabetes Mellitus as a monotherapy adjunct to diet and exercise.

4.2 Posology and method of administration

The usual adult dose for oral use is 20 mg of Teneligliptin once daily. In case of insufficient effect, dosage can be increased to 40 mg once time daily while closely monitoring the clinical progress.

4.3 Contraindications

- 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 (since a prompt correction of hyperglycaemias is required) with infusion and insulin.
- Severe trauma before and after surgery and when the blood glucose level is controlled with insulin injection.

4.4 Special warnings and precautions for use

Careful administration recommended in:

- Patient with severe hepatic dysfunction as there is no usage experience and safety has not been established.
- Patient with heart failure (NYHA class III~IV) as there is no usage experience and safety has not been established.

- Patient under sulfonyl urea medication or Insulin formulations risk of hypoglycemia may increase
- Hypoglycemia may occur in patients with:
  - Adrenal insufficiency
  - Malnutrition, starved state, irregular dietary intake, insufficient dietary intake or hyposthenia
  - Vigorous muscular movement
  - Patient with excessive alcohol consumption
- Patient with history of abdominal surgery or intestinal obstruction (intestinal obstruction might occur).
- 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 hypokalaemia.
- Acute pancreatitis has been reported in studies and since acute pancreatitis is also reported with similar molecules, 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.

Important Precautions:

- The points regarding hypoglycaemia and its coping strategy should be sufficiently explained to the patient when using Teneligliptin. Particularly, when coadministered with sulfonylurea or insulin formulation, there is a possibility of higher risk of hypoglycemia. In order to reduce the risk of hypoglycemia caused by sulfonylurea o insulin formulation, consider decreasing the dose of sulfonylurea or insulin formulation when given in combination with teneligliptin.
- Consider its use 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.
- Consider the application of Teneligliptin in patients who have not sufficiently responded to diet and exercise therapy, which is a basic treatment for diabetes.
- During administration of Teneligliptin, regularly check the blood sugar; check the effect of the drug. In case, the drug effect is insufficient even after taking this Teneligliptin for 3 months, then change to other treatment.
- During continuous administration, there are cases that do not need medication, cases where dose has to be reduced, and cases where there is no effect or inadequate response due to complications of patient's infestation and infections; and therefore, pay attention to dietary intake, blood sugar level, and presence of infections, as well as, always take care of selection of drugs, dosage, and whether to continue the drug.
- Since there is a possibility that adverse reactions, such as QT prolongation, might occur. It is desirable to avoid the medication in the patients having QT prolongation or it history (such as hereditary QT prolongation syndrome) or the patients having history of Torsade's de pointes.
- Since there is a risk of hypoglycemia, attention should be paid while administration of this drug to the patients who are engaged in car driving or working at heights.

- In regards to the co-administration of this drug and insulin formulation, the efficacy and the safety has not been studied.
- This drug and GLP-1 receptor agonist both have GLP-1 receptor mediated antihyperglycemic effect. No clinical trial results are available regarding concomitant use of both drugs; also, effectiveness and safety have not been confirmed.

Other Precautions

In reported clinical trials, QT prolongation has been reported when 160 mg of this Teneligliptin was administered once daily. (Approved dose of this Teneligliptin: The usual dosage is 20 mg of teneligliptin once daily and the maximum dose is 40 mg once daily). When a repeated oral dose of 40 mg or 160 mg teneligliptin once daily to the healthy adults for four days, the maximum mean value (and 90% confidence interval upper limit) of placebo-corrected QTcI (QTc corrected per individual) interval change was 3.97 at 3 hours after dosing completion in 40 mg group and 9.3 msec at 1.5 hours after dosing completion in 160 mg group.

In a reported 52-week repeated oral administration toxicity test using cynomolgus monkey, the cutaneous symptoms, such as superficial abrasion, scab, or ulcer, were observed on the tail, extremities, and auricles with the dose of 75mg/kg/ day. AUC_{0-24hr} in this case reached to around 45 times when 40 mg/day was administered to humans. Note that the same toxicity findings have not been reported in other animal species (rats, mice, and rabbits) and humans**.**

4.5 Drugs interactions

Drug name and other details	**Clinical symptoms and treatment methods**	**Mechanism and Risk factors**
Medicines for diabetic disease: ☐ Sulfonylurea ☐ Fast-acting insulin secretagogue α-glucosidase inhibitor ☐ Biguanides drugs ☐ Thiazolidine drug ☐ GLP-1 analogue preparation ☐ SGLT2 inhibitor insulin preparation	Since hypoglycemia might occur, these drugs should be administered while carefully monitoring 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 risk of hypoglycaemia is observed, usually, cane sugar should be given and when coadministered with α-glucosidase inhibitor, glucose should be given.	Hypoglycemic action is Increased.
Drugs increasing hypoglycaemic 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 hypoglycaemic 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 cause QT prolongation Class IA antiarrhythmic drug Quinidine Sulphate 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.

Glimepiride combination:

Reportedly, when a repeated dose of 1 mg glimepiride for four days and a single combined dose (2nd day of glimepiride administration) of 40 mg teneligliptin were administered to the healthy adults (16), the ratio (90% confidence interval) of Cmax of teneligliptin and AUC0-∞ geometric mean value was 0.971 (0.866- 1.088) and 0.926 (0.894-0.959) with respect to single-dose administration of Teneligliptin alone. Furthermore, when a repeated-dose of 40 mg teneligliptin for seven days and a single combined dose (7th day of teneligliptin administration) of 1 mg glimepiride were administered to the healthy adults, the ratio (90% confidence interval) of Cmax of glimepiride and AUC0-∞ geometric mean value was 1.016 (0.932 - 1.106) and 1.023 (0.978 - 1.071) with respect to single-dose administration of glimepiride alone.

Pioglitazone combination:

Reportedly, when a repeated dose of 40 mg pioglitazone for eight days and a repeated combined dose (6^{th} to 8th day of pioglitazone administration) of 850 mg teneligliptin were administered to the healthy adults, the ratio (90% confidence interval) of Cmax of teneligliptin and AUC0-24hr geometric mean value was 0.907 (0.853 –0.965) and 1.042 (0.997 - 1.089) with respect to single-dose administration of teneligliptin alone.

Furthermore, when a repeated-dose of 40 mg teneligliptin for (6^{th} to 8th day of pioglitazone administration) of 850 mg teneligliptin of 850 mg metformin were administered to the healthy adults, the ratio (90% confidence interval) of C_{max} of pioglitazone and $AUC_{0-\infty}$ geometric mean value was 1.004 (0.917 - 1.100) and 1.134 (1.060-1.213) with respect to single-dose administration of pioglitazone alone. Similarly, the ratio (90% confidence interval) of Cmax of active metabolites (M-III and M-IV) of pioglitazone and $AUC_{0-12\ hr}$ geometric mean value was 1.057 (0.974 - 1.148) and 1.206 (1.143 - 1.278) with respect to reported dose administration of metformin only, and $AUC_{0-12\ hr}$ of Metformin increased 20.9 % due to co administration.

Metformin combination:

Reportedly, when a repeated dose of 40 mg teneligliptin once daily for eight days and a repeated combined dose (6^{th} to 8^{th} day of teneligliptin administration) of 850 mg metformin twice daily

were administered to the healthy adults, the ratio (90% confidence interval) of Cmax of teneligliptin and $AUC_{0\text{-}24hr}$ geometric minimum mean-square value was 0.907 (0.853 - 0.965) and 1.042 (0.997 - 1.089) with respect to repeated-dose administration of teneligliptin only.

Furthermore, when a repeated combined dose (4th to 8th day of metformin administration) of 850 mg metformin twice daily for eight days and 40 mg teneligliptin once daily was administered to the healthy adults, the ratio (90% confidence interval) of Cmax of metformin and AUC0-12hr geometric minimum mean-square value was 1.057 (0.974 - 1.148) and 1.209 (1.143 - 1.278) with respect to repeated-dose administration of teneligliptin alone, and it increased to 37% and 49% due to co-administration of metformin only, and the AUC0-12hr of metformin increased 20.9% due to coadministration).

Ketoconazole combination:

Reportedly, when a repeated dose of 400 mg ketoconazole for six days and a single combined does (4^{th} day of ketoconazole administration) of 20 mg teneligliptin were administered to the healthy adults, the ratio (90% confidence interval) of C_{max} of teneligliptin and $AUC0\text{-}_{0\text{-}12\ hr}$ geometric minimum mean-square value was 1.37 (1.25 - 1.50) and 1.49 (1.39 - 1.60) with respect to single-dose administration of teneligliptin alone, and it increased to 37% and 49% due to co-administration.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

Teneligliptin should be used in pregnant women or in women who may possibly be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment. The safety of this Teneligliptin in pregnant women has not been established. Furthermore, the transfer to embryo in animal studies (rats) has been reported in literature.

Breast-feeding

Breast-feeding must be discontinued during administration of this Teneligliptin in lactating women (transfer to milk in animal studies (rats) has been reported in literature.

Pediatric Use

The safety of this Teneligliptin in low birth weight baby, new-born baby, infant, or little child has not been established.

Geriatric Use

In general, elderly patients often have physiological hypo function; 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. Thus, no dose adjustment is proposed in mild to moderate hepatic impaired patients. As per reported data, there was no clinical experience in severe degree hepatic impairment**.**

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been reported. However, patients should be alerted to the risk of hypoglycaemia especially when Teneligliptin coadministered with sulphonylureas and/or insulin.

4.8 Undesirable effects

The most frequent individual adverse event was hypoglycemia, dizziness, headache, constipation, diarrhoea and pyrexia. Most of the adverse events are mild in severity.

a) Hypoglycemia

b) Intestinal Obstruction (0.1%)

c) Liver dysfunction (unknown frequency)

d) Interstitial pneumonia (frequency unknown)

(1) Significant adverse reactions:

a) Hypoglycemia: Hypoglycemia may occur when co-administered with other drugs for diabetes (in combination with glimepiride: 8.9%, in combination with pioglitazone: 1.5%, in combination with glinides: 3.8%, in combination with Biguanides: 1.1%, and in combination with α-glucosidase inhibitor: 1.3%). Particularly, a severe hypoglycemia is noted when co-administered with other DPP-4 inhibitors, sulfonylurea, and also the cases with loss of consciousness are reported; and therefore, consider decreasing the quantity of sulfonylurea when co-administered with sulfonylurea. Furthermore, hypoglycemia (1.1%) is also reported when not co-administered with other drugs for diabetes. In case hypoglycemia is observed, appropriate measures must be taken such as intake of carbohydrate containing food.

b) Intestinal Obstruction (0.1%): Intestinal obstruction may occur; and therefore, the patient should be carefully monitored.

If any abnormal findings, such as severe constipation, abdominal swelling, continuous abdominal pain, and vomiting, are observed, administration should be discontinued and appropriate measures must be taken.

c) Liver dysfunction (unknown frequency): Liver dysfunction occurs with increase in AST (SGOT), ALT (SGPT); and therefore, appropriate measures such as performing sufficient monitoring of these parameters should be taken. Discontinue teneligliptin if abnormalities are observed.

d) Interstitial pneumonia (frequency unknown): Interstitial pneumonia may occur. If coughing, breathing difficulty, onset of fever, and abnormal chest sounds (crepitation) are noticed, the examinations such as chest X-ray, chest CT, and serum maker should be carried out. In case interstitial pneumonia is suspected, the appropriate measures like discontinuation of administration and administration of adrenocortical hormone should be taken.

Other Adverse reactions

Incidence/Types 0.1% ~ 1% < 0.1%

If adverse reactions are observed, the drug administration should be discontinued and appropriate measures should be taken.

Digestive system: Constipation, abdominal swelling, abdominal discomfort, nausea, stomach ache, flatulence, stomatitis, gastric polyp, colon polyp, duodenal ulcer, reflux esophagitis, diarrhea, anorexia, increased amylase, increased lipase, acute pancreatitis

Liver: Increased AST (GOT), increased ALT (GPT), and increased γ-GTP and rise in Al-P

Kidney and urinary system: Albuminuria, positive ketone body in urine

Skin: Eczema, Wet rash, pruritus, allergic dermatitis

Others: Increased CK (CPK), increased serum potassium, fatigue, allergic, rhinitis, and increased serum uric acid

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

4.9 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.

5. Pharmacological properties

5.1 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.

5.2 Pharmacodynamics properties

DPP-4 inhibitory action and GLP-1 degradation inhibitory action

- Teneligliptin inhibits concentration-dependent human plasma DPP-4 activity, and its IC50 value (95% confidence interval) was 1.75 (1.62 - 1.89) nmol/L (in vitro).
- Teneligliptin concentration-dependently suppressed the degradation of GLP-1 in rat plasma, with IC50 values and its 95% CI being 2.92 nM [2.21, 3.87] (in vitro).
- In the glucose tolerance test using Zucker Fatty rat, an obesity model showing insulin resistance and abnormal glucose tolerance, teneligliptin increased plasma active GLP-1 concentration and plasma insulin concentration by its single dose administration.
- In patients having type 2 diabetes mellitus, the administration of 20 mg teneligliptin once daily inhibited the plasma DPP4 activity and increased the plasma active GLP-1 concentration.

Glucose tolerance improvement action

- In the glucose tolerance test using Zucker Fatty rat, an obesity model showing insulin resistance and abnormal glucose tolerance, teneligliptin controlled an increase in the blood sugar level by its single-dose administration
- In patients having type 2 diabetes mellitus, the administration of 20 mg teneligliptin once daily improved the blood sugar after breakfast, lunch, and dinner and the fasting blood sugar.

5.3 Pharmacokinetic properties Plasma concentration:

Single-dose administration:

In a reported study, the plasma concentration changes and the pharmacokinetic parameters of teneligliptin after a single oral dose of 20 mg and 40 mg of teneligliptin given empty stomach to the healthy adults are shown below.

Pharmacokinetic parameters at the time of single - dose oral drug administration in healthy adults

Strength	**C (ng/mL)**	**AUC (ng.hr/mL)**	**tmax (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	3705.0 ± 787.0	1.0 (0.5 3.0)	20.8

n=6, Mean Value ± SD

T_{max} = Central value (minimum value - maximum value)

Repeated dose administration**:**

In the reported study the pharmacokinetic parameters of teneligliptin after a repeated dose of 20 mg of teneligliptin once daily for seven days given 30 minutes before breakfast to the healthy adults are shown below. It was thought that the state of equilibrium will be attained within seven days

Pharmacokinetic parameters at the time of repeated - dose oral drug administration in healthy adults

	Cmax (ng/mL)	**AUC0-24 hr (ng.hr/mL)**	**AUC0-inf (ng.hr/mL)**	**tmax (hr)**	**t1/2 (hr)**
After first 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 (0.4-2.0)	30.2±6.9

n=7, Mean Value ± SD

Tmax = Central value (minimum value - maximum value)

Influence of meal to drug Absorption

Cmax decreased after a single dose of 20 mg of teneligliptin given post meal to the healthy adults as compared to empty stomach and tmax prolonged from 1.1 hr to 2.6 hr; however, no difference observed in AUC.

Pharmacokinetic parameters at the time of fasting and after food intake in healthy adults

	Cmax (ng/mL)	**AUC0-24 hr (ng.hr/mL)**	**AUC0-inf (ng.hr/mL)**	**tmax (hr)**	**t1/2 (hr)**
Empty Stomach	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)
Post Meal	184.9 (187.5±33.55)	1806 (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 value ± Standard Deviation)

Tmax = Arithmetic **mean value ± Standard Deviation**

Rate of protein binding:

The protein binding ratio was 77.6 to 82.2% when the [ng/mL) was added to the human plasma (*in vitro*).

Metabolism

Following a single oral administration of 20 mg [^{14}C] label teneligliptin to the healthy adults, the unaltered substance and the metabolites M1, M2, M3, M4, and M5 were observed in the blood plasma. Furthermore, the ratio of $AUC_{0-\infty}$ of teneligliptin, M1, M2, M3, M4, and M5 with respect to $AUC_{0-\infty}$ calculated from the plasma radioactive concentration up to 72 hours after administration was 71.1%, 14.7%, 1.3%, 1.3%, 0.3%, and 1.1%.

Mainly, CYP3A4 and Flavin-containing monooxygenases (FMO1 and FMO3) participate in the metabolism of teneligliptin. Furthermore, although teneligliptin showed a weak inhibitory action towards CYP2D6, CYP3A4, and FMO (IC50 value:

489.4, 197.5, and 467.2μmol/L), it did not show inhibitory action towards CYP1A2, CYP2A6, CYP2B6, 1) CYP2C8, CYP2C8/9, CYP2C19, and CYP2E1, and CY P1A2 and CYP3A4 were not introduced (in vitro).

Excretion:

When a single oral dose of 20 mg and 40 mg 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 39 mL/hr/kg.

When a single oral dose of 20 mg [^{14}C] label 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. Furthermore, with respect to the dosage up to 120 hours after administration, the accumulated urinary excretion rate of unaltered substance, M1, M2, and M3 was 14.8%,17.7%, 1.4%, and 1.9%, respectively and the accumulated feces excretion rate of unaltered substance, M1, M3, M4, and M5was26.1%, 4.0%, 1.6%, 0.3%, and 1.3%, respectively.

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, (IC50 value: 99.2μmol/L); however, it did not show inhibitory action towards OAT 1 and organic cation transporter OCT2 (in vitro).

Renal dysfunction

When a single oral dose of 20 mg teneligliptin was given to the renal dysfunction patients, no remarkable change was observed in Cmax andt1/2 of teneligliptin depending on the extent/degree of renal dysfunction. On the other hand, in the mild renal dysfunction patient (Ccr ≥50 to ≥80mL/min), moderate renal dysfunction patient (Ccr ≥30 to ≥50mL/min), and severe renal dysfunction patient (Ccr<30mL/min), the AUC0∞ was found to be about 1.25 times, 1.68 times, and 1.49 times, respectively, as compared to the healthy adults, and AUC0-43hr of terminal renal failure affected individual was about 1.16 times as compared to the healthy adults. Furthermore, 15.6% of teneligliptin dose was removed due to haemodialysis.

When a single oral dose of 20mg teneligliptin was given to the hepatic dysfunction patients, the Cmax of teneligliptin was found to be about 1.25 times and 1.38 times and AUC0-∞ was about 1.46 times and 1.59 times, respectively, in mild hepatic dysfunction patient (total score 5~6 by Child-Pugh classification) and moderate hepatic dysfunction patient (total score 7~9 by Child-Pugh classification) as compared to the healthy adults. There is no clinical experience in high degree hepatic dysfunction patient (total score more than 9 by Child-Pugh classification).

Pharmacokinetics in Elderly Patient

When a single oral dose of 20 mg teneligliptin was given to the healthy elderly patients (≥65 years old ≤75 years old, 12 patients) and non-elderly patients (≥45 years old ≤65 years old, 12 patents) on empty stomach, the ratio (90% confidence interval) of geometric minimum mean-square value of elderly patient with Cmax, $AUC_{0-\infty}$, and $t_{1/2}$ of non-elderly patient was almost similar, 1.006 (0.871- 1.163), 1.090 (0.975 - 1.218), and 1.054 (0.911-1.219), respectively.

6. Nonclinical properties

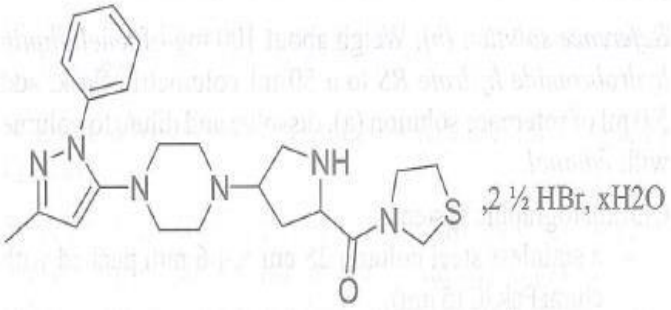
6.1 Animal Toxicology or Pharmacology

Teneligliptin was non carcinogenic in rats and mice carcinogenicity assays. In reported 104-week oral carcinogenicity assay in rats, the NOAEL was 75 mg/kg/day in males and 100 mg/kg/day in females [18 and 24 times, respectively the maximum clinical daily dose (40 mg/day) on a mg/m2 basis] for neoplastic changes. In reported 26-Week oral carcinogenicity assay in CB6F1-Tg rasH2 mice, the NOAEL was 600 mg/kg/day (73 times the maximum clinical daily dose on a mg/m2 basis) for neoplastic changes. Teneligliptin was not genotoxic in various reported in vitro (bacterial reverse mutation tests, unscheduled DNA synthesis test in liver cells and chromosomal aberration test with cultured mammalian cells) and in vivo (bone marrow micronucleus tests in rats) genotoxicity assays. Teneligliptin reported effects on fertility of both male (low epididymal weight, low number of sperms in the epididymal tail, and high percentage of abnormal sperms) and female (low number of implantation and live fetuses and high rate of early embryonic death) rats. In male and female rats the NOAEL was 70 and 100 mg/kg/day (17 and 24 times, respectively the maximum clinical daily dose on a mg/m2 basis), respectively for reproductive function, and early embryogenesis. Teneligliptin did not report teratogenic effects in rats and rabbits. The NOAEL of 30 mg/kg/day (7 and 15 times, respectively the maximum clinical daily dose on a mg/m2 basis) was determined for embryo-fetal development in both rats and rabbits. In reported pre- and post-natal developmental study in rats, except for a decrease in food consumption (maternal animals) and body weight gain (F1 pups) no other effects were noted at the highest 100 mg/kg/day. The NOAEL was 30 mg/kg/day (7 times the maximum clinical daily dose on a mg/m2 basis).

7. Description

Teneligliptin Hydrobromide Hydarte is {(2S,4S,-4-[4-(3-methyl-1-phenyl-1H-pyrazol-5yl)piperazine-1-yl]pyrrolidine-2-yl}(1,3-thiazolidine-3-yl)methanone hemipentahydrobromide

hydrate. The empirical formula is ($C_{22}H_{30}N_6OS, 2^{1/2}$ HBr, xH_2O and its molecular weight is 628.9 g/mol. The chemical structure of Teneligliptin Hydrobromide Hydrate is:



Teneligliptin Tablets IP 20 mg is a red to pale red coloured, circular, biconvex film coated tablets plain on both sides.

The excipients used are Lactose, Talc, Colloidal Silicon Dioxide, Croscarmellose Sodium, Magnesium Stearate, Microcrystalline Cellulose, Hydroxy Propyl Methyl Cellulose, Isopropyl Alcohol, Red Oxide of Iron & Titanium Dioxide coated Mica pearlescent pigment.

8. Pharmaceutical particulars

8.1 Incompatibilities:

Not Applicable

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

AFOGLIP is available in 10 Blister strips of 10 tablets each.

8.4 Storage and handing instructions

Store in a dry, well ventilated place at a temperature not exceeding 30°C.

9. Patient Counselling Information

Package leaflet: Information for the user
AFOGLIP

Teneligliptin Tablets IP 20 mg

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 9.4.

What is in this leaflet?

9.1 What AFOGLIP are and what they are used for

9.2 What you need to know before you use AFOGLIP

9.3 How to use AFOGLIP

9.4 Possible side effects

9.5 How to store AFOGLIP

9.6 Contents of the pack and other information

9.1. What AFOGLIP are and what they are used for.

AFOGLIP contains active ingredient Teneligliptin which is an anti-diabetic drug belonging to the class DPP-4 inhibitors.

Insulin is a hormone produced by the pancreas that makes your body take in glucose (sugar) from the blood. Your body uses glucose to produce energy or stores it for future use.

If you have diabetes, your pancreas does not make enough insulin or your body is not able to use properly the insulin it produces. This leads to a high level of glucose in your blood. AFOGLIP helps to lower your blood glucose to as normal a level as possible.

AFOGLIP is indicated for the treatment of type 2 diabetes mellitus (T2DM) as a monotherapy adjunct to diet and exercise.

9.2. What you need to know before you use AFOGLIP Do not use AFOGLIP if:

- you are allergic to AFOGLIP or to any of the other ingredients of this medicine.
- you have uncontrolled diabetes, with, for example, severe hyperglycaemia (high blood glucose), nausea, vomiting, diarrhoea, rapid weight loss, lactic acidosis or ketoacidosis. Ketoacidosis is a condition in which substances called 'ketone bodies' accumulate in the blood and which can lead to diabetic pre-coma. Symptoms include stomach pain, fast and deep breathing, sleepiness or your breath developing an unusual fruity smell.
- you need to have or had a major surgery.

Warning and Precautions

- Co-administration of sulfonylurea medication or insulin formulation (Risk of hypoglycemia may increase).
- Adrenal insufficiency
- Malnutrition, starved state, irregular dietary intake, insufficient dietary intake or hyposthenia, vigorous muscular movement
- Patient with excessive alcohol consumption
- Patient with history of abdominal surgery or intestinal obstruction (intestinal obstruction might occur). 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 hypokalaemia.

Taking other medicines

Please tell your healthcare provider if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Blood sugar level may decrease when taken with other drugs for diabetes (in combination with glimepiride, pioglitazone, glinides, biguanides, and with αglucosidase inhibitor. Particularly, a severe decrease in blood sugar level is noted when taken with sulfonylurea and also the cases

with loss of consciousness are reported; and therefore, consider decreasing the quantity of sulfonylurea when taken with sulfonylurea). Furthermore, decrease in blood sugar level is also reported when not coadministered with other drugs for diabetes. In case decrease in blood sugar level is observed, appropriate measures must be taken such as intake of carbohydrate containing food.

Drugs increasing the action of AFOGLIP:

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.

- β-blocking agents
- Salicylic acid drugs
- Monoamine oxidase inhibitor

Drugs decreasing the action of AFOGLIP:

Since the blood sugar may Increase, these drugs should be administered while carefully observing the patient's condition in addition to blood sugar level.

- Adrenaline
- Adrenocortical hormone
- Thyroid hormone

Drugs known to cause QT prolongation (measure of delayed ventricular repolarisation)

It means the heart muscle takes longer than normal to recharge between beats. It is an electrical disturbance which can be seen on an electrocardiogram (ECG).

QT prolongation is seen with single administration of these drugs.

- Class IA anti-arrhythmic drug (Quinidine Sulphate Hydrate, Procainamide Hydrochloride)
- Class III antiarrhythmic drugs (Amiodarone Hydrochloride, Sotalol Hydrochloride)

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, you should not take these tablets. Ask your healthcare provider for advice before taking any medicine. **Driving and using machines**

These tablets may cause drowsiness and make you sleepy. Do not drive or operate machinery until you know how this product affects you.

9.3.How to use AFOGLIP

AFOGLIP will be given to you by a health care provider.

- Always use these tablets exactly as your health care provider has told you.
- You should check with your health care provider if you are unsure of the instructions.
- These tablets should preferably be taken after meals.

How much will be given

Your health care provider will decide how much to give you.

If you take more tablets than you should

You should contact your health care provider if you experience any of these effects and you may be admitted to hospital for appropriate treatment, if necessary.

If you have any further questions on the use of this product, ask your health care provider.

9.4.Possible side effects

Like all medicines, these tablets can cause side effects, although not everybody gets them. They may happen hours or days after you have taken the tablets. There is no clear information on how often side effects occur after taking this medicine. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your health care provider.

The most frequently observed adverse events are:

- Hypoglycemia (decrease in blood sugar level),
- Dizziness (Vertigo)
- Headache
- Diarrhea
- Pyrexia (increased body temperature).

Most of the adverse events were mild in severity.

Intestinal obstruction may occur; and therefore, you should be carefully monitored. If you have symptoms such as severe constipation, abdominal swelling, continuous abdominal pain, and vomiting, are observed, you should consult your doctor.

If you are diagnosed with liver dysfunction, consult your doctor. Your doctor may ask you to stop AFOGLIP.

Interstitial pneumonia may occur. If coughing, breathing difficulty, onset of fever, and abnormal chest sounds (crepitation) are noticed, your doctor may suggest examinations such as chest X-ray, chest CT, and serum maker. In case interstitial pneumonia is suspected, your doctor may discontinue the AFOGLIP.

Other adverse reactions/side effects:

If adverse reactions are observed, the drug administration should be discontinued and appropriate measures should be taken.

Digestive system: Constipation, abdominal swelling, abdominal discomfort, nausea, stomach ache, flatulence (passing wind), inflammation of the mouth and lips, gastric polyp (abnormal growths on the inner lining of your stomach), colon polyp (an abnormal growth of tissue in the lining of the bowel), a crater (ulcer) in the lining of the beginning of the small intestine, reflux esophagitis (inflammation or irritation of the esophagus when the stomach contents and acids back up into the esophagus.), diarrhea, anorexia and increased amylase, lipase which shows damage to your pancreas.

Liver: Increased AST and ALT (very high Alanine aminotransferase and Aspartate Aminotransferase are most commonly due to viral hepatitis, ischemic hepatitis, or liver injury due to drug or toxin).

Kidney and urinary system: Albuminuria (a sign of kidney disease and means that you have too much albumin in your urine).

Positive ketone body in urine (If your cells don't get enough glucose, your body burns fat for energy instead. This produces a substance called ketones, which can show up in your blood and urine. High ketone levels in urine may indicate diabetic ketoacidosis (DKA), a complication of diabetes that can lead to a coma or even death)

Skin: Eczema, rash, pruritus, allergic dermatitis

Others Increased Creatine Kinase may indicate injury or stress to muscle tissue, of heart, or the brain, increased serum potassium, fatigue, allergic, rhinitis, and increased serum uric acid (dysfunction of kidney).

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How to store AFOGLIP

Store in a dry, well ventilated place at a temperature not exceeding 30°C

9.6 Contents of the pack and other information

The active ingredient is Teneligliptin Hydrobromide Hydrate and the excipients used are Lactose, Talc, Colloidal Silicon Dioxide, Croscarmellose Sodium, Magnesium Stearate, Microcrystalline Cellulose, Hydroxy Propyl Methyl Cellulose, Isopropyl Alcohol, Red Oxide of Iron & Titanium Dioxide coated Mica pearlescent pigment.

10. Details of manufacturer

Glenmark Pharmaceuticals Ltd.

Samlik Marchak,

Industrial Growth Centre,

East Sikkim, Sikkim – 737 135

11. Details of permission or licence number with date

Mfg Lic No M/602/2012 issued on 14 Jan 2021

12. Date of revision

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MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/AFOGLIP 20mg/APR-21/03/PI