Teneligliptin Tablets 20 mg
Olymprix

1. NAME OF THE MEDICINAL PRODUCT
Olymprix

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:
Olymprix
Each film-coated tablet contains:
Teneligliptin hydrobromide hydrate equivalent to
Teneligliptin……..20 mg
Excipients……q.s.

3. PHARMACEUTICAL FORM
Film-coated tablet

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
For the treatment of type 2 diabetes mellitus as a monotherapy; adjunct to diet and Exercise
4.2 Posology and method of administration
Posology
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. Reported evidences suggests that, there are no major problems in increasing the dose to 40 mg as appropriate, provided that the necessity of the dose increase is judged carefully based on thorough observation of the blood glucose control and safety of the patient receiving teneligliptin 20 mg.
Special Populations
Pediatric Use: The safety of this product in low birth weight baby, newborn baby, infant, or little child has not been reported. (No usage experience).
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. Thus no dose adjustment is proposed in mild to moderate hepatic impaired patients. There was no clinical experience in severe degree hepatic dysfunction patient.
4.3 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 type 1 diabetes
- Severe trauma, before and after surgery and in severe infections.

4.4 Special warnings and precautions for use
1. Careful Administration (this medicine should be carefully administered in the following patients):

1) Patient with severe hepatic dysfunction (as there is no usage experience and safety has not been established).
2) Acute pancreatitis has been observed in studies done outside Japan 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.
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).
5) 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
6) Patient with history of abdominal surgery or intestinal obstruction (intestinal obstruction might occur).
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

2. Important Precautions:

1) The points regarding hypoglycemia and its coping strategy should be sufficiently explained to the patient when using this product. 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 hypoglycemia caused by sulfonylurea or insulin formulation, consider decreasing the dose of sulfonylurea or insulin formulation when given in combination with teneligliptin.
2) 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.
3) Consider the application of this product: in patients who have not sufficiently responded to diet and exercise therapy, which is a basic treatment for diabetes.
4) 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.
5) 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.
6) 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 its history (such as hereditary QT prolongation syndrome) or the patients having history of Torsade's de pointes.
7) 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.
8) In regards to the co-administration of this drug and insulin formulation, the efficacy and the safety have not been studied.
9) This drug and GLP-1 receptor agonist both have GLP-1 receptor mediated anti-hyperglycemic effect. No clinical trial results are available regarding concomitant use of both drugs; also, effectiveness and safety have not been confirmed.

3. Other Precautions

1) QT prolongation has been reported when 160 mg of this product was administered 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 3.9 (7.6) msec at 3 hours after dosing completion in 40 mg group and 9.3 (13.0) msec at 1.5 hours after dosing completion in 160 mg group).
2) The cutaneous symptoms, such as superficial abrasion, scab, or ulcer, were reported on the tail, extremities, and auricles of cynomolgus monkey with the dose of 75mg/kg/ day. AUC0-24hr in this case reached to around 45 times when 40 mg/day was administered to humans. Same toxicity findings have not been reported in other animal species (rats, mice, and rabbits) and humans.

4.5 Interaction with other medicinal products and other forms of interaction

Table 1: Precautions for Coadministration with certain drugs

Drug name and other details	**Clinical symptoms and treatment methods**	**Mechanism and Risk factors**
Medicines for diabetic disease: Drugs for diabetes - Sulfonylureas - fast-acting insulin secretagogues - α-glucosidase inhibitors - Biguanide drugs - Thiazolidinediones - GLP-1 analog preparations - SGLT2 inhibitors - Insulin preparations	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 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	Hypoglycemic action is increased.
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 cause QT prolongation - Class IA anti arrhythmic drugs: Quinidine sulfate hydrate, procainamide hydrochloride - Class III antiarrhythmic drugs: amiodarone	QT prolongation might occur.	QT prolongation is seen with single administration of these drugs.

hydrochloride, sotalol hydrochloride		

(1) Glimepiride combination:
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).

(2) Pioglitazone combination:
When a repeated dose of 30 mg pioglitazone for nine days and a single combined dose (7th day of pioglitazone administration) of 40 mg teneligliptin were administered to the healthy adults, the ratio (90% confidence interval) of Cmax of teneligliptin and AUC0-∞ geometric mean value was 1.117 (0.984 - 1.266) and 1.005 (0.967 - 1.045) with respect to single-dose administration of teneligliptin alone, and the Cmax of teneligliptin increased 11.7% due to co-administration. Furthermore, when a repeated-dose of 40 mg teneligliptin for nine days and a single combined dose (7th day of teneligliptin administration) of 30 mg pioglitazone were administered to the healthy adults, the ratio (90% confidence interval) of Cmax of pioglitazone and AUC0-∞ 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 AUC0-∞ geometric mean value was 1.041 (0.975 - 1.113) and 1.116 (1.056 - 1.180) in M-III and 1.028 (0.963 - 1.096) and 1.088 (1.032 - 1.147) in M-IV).

(3) Metformin combination:
When a repeated dose of 40 mg teneligliptin once daily for eight days and a repeated combined dose (6 to 8th 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 AUC0-24hr 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 metformin only, and the AUC0-12hr of metformin increased 20.9% due to coadministration).

(4) Ketoconazole combination:
When a repeated dose of 400 mg ketoconazole for six days and a single combined does (4th day of ketoconazole administration) of 20 mg teneligliptin were administered to the healthy adults (14), the ratio (90% confidence interval) of Cmax of teneligliptin and AUC0-∞ 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 during Pregnancy, Delivery, or Lactation

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

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

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 performed. However, patients should be alerted to the risk of hypoglycaemia especially when Teneligliptin is co-administered with sulphonylurea and/or insulin.

4.8 Undesirable effects

The most frequently reported adverse reactions were hypoglycaemia, constipation, and arthralgia. The most frequently reported individual adverse event was dizziness in Teneligliptin group (5/158) 3.2%, followed by headache in (5/158) 3.2%, diarrhea in (4/158) 2.5% and pyrexia in (4/158) 2.5%. An AE (cancer right pyriform fossa) leading to early termination from the study was reported for 1/158(0.6%) of patients in the Teneligliptin group, this was unrelated to study drug. No SAE related to the study drug was reported during the study. Most of the adverse events were mild in severity.

(1) Significant adverse reactions:

a) Hypoglycemia: Hypoglycemia may occur when co-administered with other drugs for diabetes. 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: 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, examinations such as chest X-ray, chest CT, and serum markers should be carried out. In case interstitial pneumonia is suspected, appropriate measures like discontinuation of Teneligliptin and administration of adrenocortical hormone should be done.

(2) Other adverse reactions/side effects:

Table 2: Other Adverse reactions

Incidence/Types	**0.1% ~ 1%**	**<0.1%**
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	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	

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 Pharmacodynamic properties

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 form GLP-1

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

1. 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).
2. 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).
3. In the glucose tolerance test using Zucker Fatty rat, an obesity model showing insulin resistance and abnormal glucose tolerance, teneligliptin increased plasma active form GLP-1 concentration and plasma insulin concentration by its single-dose administration.
4. In patients having type 2 diabetes mellitus, the administration of 20 mg teneligliptin once daily inhibited the plasma DPP-4 activity and increased the plasma active form GLP-1 concentration.

Glucose tolerance improvement action

1. 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
2. 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

Clinical Study

In a double-blind, randomized, comparative study of 16 week treatment duration Teneligliptin Tablets were compared with Placebo Tablets in the treatment of patients with type 2 diabetes mellitus inadequately controlled on diet and exercise alone. A total of 237 subjects (age of 48.9-49.6 years) were enrolled in the study and randomized to treatment with 158 patients in the Teneligliptin Tablets group, and 79 patients Placebo Tablets group. All subjects were Asian (Indian) and 60.8% were male and 39.2% were female. There was a statistically significant difference ($p<0.05$) for the primary end point, mean change in HbA1c from

baseline to end of treatment in both ITT (change in HbA1c: 0.555) and PP (change in HbA1c: 0.642) population. There was also statistical significant difference ($p<0.05$) for proportion of patients with HbA1c below 7% between Teneligliptin and Placebo tablets in both PP (43.6%) and ITT (43.4%) population.

5.2 Pharmacokinetic properties

Plasma concentration:

(1) Single – dose administration:

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.

Table 3: Pharmacokinetic parameters at the time of single - dose oral drug administration in healthy adults

Strengths	C_{max} (ng/mL)	$AUC_{0\text{-}inf}$ (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	3705.0 ± 787.0	1.0 (0.5 – 3.0)	20.8 ± 3.2

n=6, Mean Value + SD t_{max} = Central value (minimum value - maximum value)

(2) Repeated – dose administration:

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

Table 4: Pharmacokinetic parameters at the time of repeated - dose oral drug administration in healthy adults

	C_{max} (ng/mL)	$AUC_{0\text{-}24\ hr}$ (ng.hr/mL)	$AUC_{0\text{-}inf}$ (ng.hr/mL)	t_{max} (hr)	$t_{1/2}$ (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 (1.0-1.0)	30.2±6.9

n=7, Mean Value + SD t_{max} = Central value (minimum value - maximum value)

(3) Food effect:

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

Table 5: Pharmacokinetic parameters at the time of fasting and after food intake in healthy adults

	C_{max} (ng/mL)	$AUC_{0\text{-}72\ hr}$ (ng.hr/mL)	$AUC_{0\text{-}inf}$ (ng.hr/mL)	t_{max} (hr)	$t_{1/2}$ (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	1806	2044.0	2.6±1.1	26.9

	(187.5±33.55)	(1814.6±183.3)	(2056.1±230.9)		(28.3±9.5)

n=14, Geometric mean (Arithmetic mean value ± Standard Deviation) t_{max} = Arithmetic mean value ± Standard Deviation

Rate of protein binding:

The protein binding ratio was 77.6 to 82.2% when the [^{14}C] label teneligliptin (20, 100, and 500 ng/mL) was added to the human plasma (*in vitro*).

Metabolism:

1) 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%.
2) 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, CYP2C8, CYP2C8/9, CYP2C19, and CYP2E1, and CY P1A2 and CYP3A4 were not introduced (in vitro).

Excretion:

1) 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.
2) 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 M5 was 26.1%, 4.0%, 1.6%, 0.3%, and 1.3%, respectively.
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, (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 C_{max} and $t_{1/2}$ 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 $AUC_{0-\infty}$ was found to be about 1.25 times, 1.68 times, and 1.49 times, respectively, as compared to the healthy adults, and AUC_{0-43hr} 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 hemodialysis.

Liver dysfunction:

When a single oral dose of 20 mg teneligliptin was given to the hepatic dysfunction patients, the C_{max} of teneligliptin was found to be about 1.25 times and 1.38 times and $AUC_{0-\infty}$ 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 C_{max}, $AUC_{0-\infty}$, 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.

5.3 Preclinical safety data

Reported evidences suggests that, teneligliptin was non carcinogenic in rats and mice carcinogenicity assays. Teneligliptin was not genotoxic in various 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.

6. PHARMACEUTICAL PARTICULARS

6.1 Shelf-life

24 months from the date of manufacturing.

6.2 Special Precautions for Storage

Store below 25^0C away from direct sunlight.

Keep the medicine out of reach of children.

6.3 Nature and Contents of Container

10 Strips of 10 Tablets Each

7. MARKETED BY

Alkem Laboratories Ltd.
ALKEM HOUSE,
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Mumbai - 400 013. INDIA.

8. DATE OF PREPARATION/REVISION OF THE TEXT

27/04/2016