Teneligliptin Tablets 20 mg and Metformin Hydrochloride 500/1000 mg Extended Release Tablets
Olymprix M 500/ Olymprix M 1000

1. NAME OF THE MEDICINAL PRODUCT

Olymprix M 500/ Olymprix M 1000

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Olymprix M 500

Each uncoated bilayer tablet contains:
Teneligliptin hydrobromide hydrate equivalent to
Teneligliptin……..20 mg
Metformin Hydrochloride IP.....500 mg (As Extended Release)
Excipients……q.s.

Olymprix M 1000

Each uncoated bilayer tablet contains:
Teneligliptin hydrobromide hydrate equivalent to
Teneligliptin……..20 mg
Metformin Hydrochloride IP.....1000 mg (As Extended Release)
Excipients……q.s.

3. PHARMACEUTICAL FORM

Uncoated bilayer tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Olymprix M is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both teneligliptin and metformin sustained release is appropriate.
Important Limitations of Use: Olymprix M should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

4.2 Posology and method of administration

Posology

Teneligliptin and metformin combination is available for oral administration as tablets containing 20 mg teneligliptin hydrobromide hydrate; 500 mg and 1000 mg metformin hydrochloride extended release. The usual adult starting dosage of Olymprix M is 20 mg teneligliptin and 500 mg metformin hydrochloride extended release administered orally once daily. If efficacy is insufficient, the teneligliptin and metformin hydrochloride extended release dose may be increased up to 40 mg and 2000 mg once daily while closely monitoring the clinical course.

Method of administration

Olymprix M should be administered with food to reduce the gastrointestinal side effects associated with the metformin component. Olymprix M should be swallowed whole. The tablets must not be split, crushed, or chewed before swallowing

Special Populations

Pediatric Use: Safety and effectiveness of Olymprix M in pediatric patients under 18 years have not been established.

Geriatric Use: As metformin is excreted via the kidney, and elderly patients have a tendency to decreased renal function, elderly patients taking Olymprix M should have their renal function monitored regularly.
Renal impairment: Olymprix M is contraindicated in renal impairment (e.g., serum creatinine levels greater than or equal to 1.5 mg/dL for men, greater than or equal to 1.4 mg/dL for women or abnormal creatinine clearance), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicaemia
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 hepatic impaired patients. There was no clinical experience of teneligliptin in severe degree hepatic dysfunction patient. The presence of liver disease is a risk-factor for the development of lactic acidosis during metformin therapy, and the drug should be avoided in patients with hepatic insufficiency.

4.3 Contraindications

Olymprix M 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.
- Renal failure or renal dysfunction (creatinine clearance < 60 mL/min), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia
- Acute or chronic disease which may cause tissue hypoxia such as: cardiac or respiratory failure, recent myocardial infarction, shock
- Hepatic insufficiency, acute alcohol intoxication, alcoholism (due to the metformin component)

Olymprix M should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials because use of such products may result in acute alteration of renal function.

4.4 Special warnings and precautions for use

General

Olymprix M should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Pancreatitis

There has been a report of pancreatitis in patient taking teneligliptin. If pancreatitis is suspected, Olymprix M should be discontinued.

Hypoglycemia

When co-administered with sulfonylurea or insulin formulation, there is a possibility of higher risk of hypoglycemia. Therefore, caution is advised when Olymprix M is used in combination with a sulfonylurea or insulin. A dose reduction of the sulfonylurea or insulin may be considered. Metformin alone does not cause hypoglycemia under usual circumstances of use, but hypoglycemia could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol.

Lactic Acidosis

Lactic acidosis is a very rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to metformin hydrochloride accumulation. Reported cases of lactic acidosis in patients on metformin hydrochloride have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by assessing other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should generally be avoided in patients with clinical or laboratory evidence

of hepatic disease. The risk of lactic acidosis must be considered in the event of non-specific signs such as muscle cramps with digestive disorders as abdominal pain and severe asthenia. Lactic acidosis is characterized by acidotic dyspnea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5mmol/L and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, metformin hydrochloride should be discontinued and the patient should be hospitalized immediately.

Renal function

The risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Therefore, Olymprix M is contraindicated in patients with renal impairment.

As metformin hydrochloride is excreted by the kidney, serum creatinine levels should be determined before initiating treatment and regularly thereafter:

- At least annually in patients with normal renal function;
- At least two to four times a year in patients with serum creatinine levels at the upper limit of normal and in elderly subjects

Decreased renal function in elderly subjects is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive therapy or diuretic therapy and when starting therapy with a non-steroidal anti-inflammatory drug.

Impaired Hepatic Function

Since impaired hepatic function has been associated with some cases of lactic acidosis, Olymprix M should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B12 Levels

In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B12 levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, is, however, very rarely associated with anaemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B12 supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on Olymprix M and any apparent abnormalities should be appropriately investigated and managed.

Certain individuals (those with inadequate Vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal Vitamin B12 levels. In these patients, routine serum Vitamin B12 measurements at two- to three-year intervals may be useful.

Administration of iodinated contrast agent

Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Therefore, in patients in whom any such study is planned, Olymprix M should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal

Hypoxic States

Cardiovascular collapse (shock), acute congestive heart failure, acute myocardial infarction and other conditions characterised by hypoxemia have been associated with lactic acidosis and may also cause pre-renal azotaemia. If such events occur in patients receiving Olymprix M therapy, the medication should be promptly discontinued.

Surgery

Metformin hydrochloride must be discontinued 48 hours before elective surgery with general, spinal or peridural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and only if normal renal function has been established.

Use with Insulin

The use of Olymprix M in combination with insulin has not been adequately studied.

Other Precautions

- 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.)
- 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.

4.5 Interaction with other medicinal products and other forms of interaction

Teneligliptin:

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	QT prolongation might occur.	QT prolongation is seen with single administration of these drugs.

- Class III antiarrhythmic drugs: amiodarone 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 AUC $_{0-\infty}$ 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 AUC $_{0-\infty}$ 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 AUC $_{0-\infty}$ 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 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$_{0-\infty}$ 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 AUC $_{0-24hr}$ 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 AUC $_{0-12hr}$ 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 AUC $_{0-12hr}$ 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 AUC $_{0-\infty}$ 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.
Metformin:

Furosemide - A single-dose, Metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration.
Nifedipine - Co-administration of nifedipine increases plasma metformin Cmax and AUC and increases the amount excreted in the urine. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.
Cationic drugs - Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose, metformin-cimetidine drug interaction studies.
Others- Certain drugs tend to produce hyperglycaemia and may lead to loss of glycaemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving Metformin, the patient should be closely observed for loss of blood glucose control.

4.6 Use during Pregnancy, Delivery, or Lactation

Teneligliptin:

The safety of teneligliptin in pregnant women has not been established. 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 teneligliptin 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 teneligliptin in lactating women (transfer to milk in animal studies (rats) has been reported.)

Metformin:

Although metformin is classified as pregnancy category B, insulin is considered the drug of choice by many experts for maintaining blood glucose levels as close to normal as possible during pregnancy. There are no adequate and well-controlled studies with sustained release metformin in pregnant women. Hence, sustained release metformin should not be used during pregnancy. In animal studies performed, metformin was detectable in milk from lactating rats. It is not known whether metformin is excreted in human milk. Because many drugs are excreted in human milk, metformin should not be administered to a nursing woman.

4.7 Effects on ability to drive and use machines

Teneligliptin:

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.

Metformin:

Metformin monotherapy does not cause hypoglycaemia and therefore has no effect on the ability to drive or to use machines. However, patients should be alerted to the risk of hypoglycaemia when metformin is used in combination with other antidiabetic agents (sulphonylureas, insulin, repaglinide).

4.8 Undesirable effects

Olymprix M:

The safety of teneligliptin combined with metformin has been evaluated in a 16-week, randomized, double-blind, placebo-controlled phase III trial involving 204 type 2 diabetic patients. Teneligliptin combined with metformin was well tolerated compared with placebo added to metformin. All of the events were classified

as mild and did not result in study discontinuation. The reported drug-related AEs in patients receiving the teneligliptin and metformin were diarrhoea, abdominal pain, hepatic steatosis, rash and edema.

Teneligliptin:

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	

Metformin:

The most common adverse events reported in clinical trials with sustained release metformin hydrochloride are: Diarrhoea, nausea and vomiting. Other commonly reported adverse events are upper respiratory tract infection, abdominal pain, distension of abdomen, constipation, flatulence, dyspepsia / heartburn, dizziness, headache and taste disturbances. Other less common adverse events with metformin are: rash/ dermatitis, lactic acidosis, asymptomatic subnormal levels of serum vitamin B12 and unpleasant metallic taste.

4.9 Overdose

Teneligliptin:

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.

Metformin:

Hypoglycaemia has not been seen with metformin hydrochloride doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose of metformin hydrochloride or concomitant risks may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Mechanism of Action:

Olymprix M:

Olymprix M tablets combine two antidiabetic medications with complementary mechanisms of action to improve glycemic control in adults with type 2 diabetes. Teneligliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor, and metformin hydrochloride sustained release, is a member of the biguanide class.

Teneligliptin:

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

Metformin:

Metformin is a biguanide that improves glycemic control in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin does not produce hypoglycemia in patients with type 2 diabetes and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

5.2 Pharmacokinetic properties

Teneligliptin:

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 (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) 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*).

Metformin:

Metformin The absolute bioavailability of a metformin 500-mg tablet given under fasting conditions is approximately 50-60%. Dose proportionality lacks due to decreasing absorption with increasing doses. Food decreases the extent and slightly delays the absorption of metformin, as shown by approximately a 40% lower mean peak plasma concentration (Cmax). Although the extent of metformin absorption (as measured by AUC) from the metformin extended release tablet increased by approximately 50% when given with food, there was no effect of food on Cmax and Tmax of metformin. Both high and low fat meals had the same effect on the pharmacokinetics of metformin ER. Maximum plasma concentration of metformin ER is achieved within 4 to 8 hours (Tmax). Peak plasma levels of metformin ER are approximately 20% lower compared to the same dose of metformin, however, the extent of absorption (as measured by AUC) is similar to metformin.

Distribution

Teneligliptin

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

Metformin

Metformin is negligibly bound to plasma proteins. Metformin has a wide volume of distribution with maximal accumulation in the small intestine. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin, steady state plasma concentrations of metformin are reached within 24-48 hours and are generally < 1 µg/mL.

Metabolism

Teneligliptin:

1) Following a single oral administration of 20 mg [14C] 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 of teneligliptin, M1, M2, M3, M4, and M5 with respect to 0-∞ AUC 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%. 0-∞
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 showed inhibitory action towards CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C8/9, CYP2C19, and CYP2E1, and CY P1A2 and CYP3A4 were not introduced (in vitro).

Metformin:

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion. Metabolism studies with extended-release metformin tablets have not been conducted.

Excretion

Teneligliptin:

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 [14C] 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, the 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 showed inhibitory action towards OAT 1 and organic cation transporter OCT2 (in vitro).

Metformin:

Tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours. The blood elimination half-life is 17.6 hours compared to approximately 6.2 hours for plasma which suggests that metformin distributes into red blood cells.

Renal dysfunction:

Teneligliptin:

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.

Metformin:

No pharmacokinetic studies of sustained release metformin have been conducted in subjects with renal insufficiency. Renal insufficiency decreases the elimination of metformin with the plasma and blood half-life, resulting in drug accumulation and an increased risk of toxicity. The renal clearance is decreased in proportion to the decrease in creatinine clearance.

Liver dysfunction:

Teneligliptin:

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).

Metformin:

No pharmacokinetic studies of sustained release metformin have been conducted in subjects with hepatic insufficiency.

Elderly Patient:

Teneligliptin:

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.

Metformin:

Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and Cmax is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

5.3 Preclinical safety data

Teneligliptin:

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.

Metformin:

There are no such studies with sustained release metformin. No evidence of carcinogenicity with metformin was found in mice and male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day. There was no evidence of mutagenic potential of metformin in in vitro and in vivo tests. Fertility of male or female rats was unaffected by metformin when administrated at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose of the metformin.

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.

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