SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINALPRODUCT

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

2. QUALITATIVE AND QUANTITATIVECOMPOSITION

1. Ziten-M 20 mg/500 mg

Each uncoated bilayer tablet contains:
Teneligliptin Hydrobromide Hydrate
Eq to Teneligliptin 20mg
Metformin Hydrochloride 1000mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Uncoated bilayer Tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ziten -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 extended release is appropriate.

Important Limitations of Use

Ziten -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

The usual adult starting dosage of **Ziten -M** is 20 mg teneligliptin and 500 mg or 1000 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.

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

Special Populations

Pediatric Use

Safety and effectiveness of **Ziten -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

Ziten-M should have their renal function monitored regularly.

Renal impairment

Assess renal function prior to initiation of **Ziten -M** and periodically thereafter.

Ziten -M is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/minute/1.73 m^2. Initiation of **Ziten -M** in patients with an eGFR between 30-45 mL/minute/1.73 m^2 is not recommended. In patients taking **Ziten -M** whose eGFR later falls below 45 mL/min/1.73 m^2, assess the benefit risk of continuing therapy. Discontinue **Ziten -M** if the patient's eGFR later falls below 30 mL/minute/1.73 m^2.

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.

4.3Contraindications

Hypersensitivity to active ingredients teneligliptin and/or metformin hydrochloride o to any of the excipients

Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma Severe trauma, before and after surgery and in severe infections.

Severe renal impairment (eGFR below 30mL/min/1.73 m^2)

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)

4.4 Special Warnings and Precautions for Use General

Ziten -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, **Ziten -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 **Ziten -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 post marketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney.

- Before initiating **Ziten -M**, obtain an estimated glomerular filtration rate (eGFR).
- **Ziten -M** is contraindicated in patients with an eGFR less than 30 mL/minute/1.73 m2. Initiation of **Ziten -M** is not recommended in patients with eGFR between 30-45 mL/minute/1.73 m2.
- Obtain an eGFR at least annually in all patients taking **Ziten -M**

A. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.

- In patients taking **Ziten -M** whose eGFR later falls below 45 mL/min/1.73 m2, assess the benefit and risk of continuing therapy.

Impaired Hepatic Function

Since impaired hepatic function has been associated with some cases of lactic acidosis, **Ziten -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 **Ziten -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

Administration of intravascular iodinated contrast agents in metformin treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop **Ziten -M** at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m2; in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and restart **Ziten -M** if renal function is stable.

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 **Ziten -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 **Ziten -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.
- There have been post marketing reports of severe and disabling arthralgia in patients taking DPP-4inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

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Interaction with other medicinal products and other forms of interaction General

Co-administration of repeated doses of teneligliptin (40 mg once daily) and metformin (850 mg twice daily) did not meaningfully alter the pharmacokinetics of either teneligliptin or metformin in healthy volunteers. Pharmacokinetic drug interaction studies with **Ziten -M** have not been performed; however, such studies have been conducted with the individual active substances of **Ziten -M**: teneligliptin and metformin.

Teneligliptin
Teneligliptin showed a weak inhibitory action towards CYP2D6, CYP3A4, (but does not inhibit other CYP isozymes) and flavin-

containing monooxygenases (FMO1 and FMO3). It is not an inducer of CYP isozymes.

Table 4: Precautions for Co-administration with certain drugs

Drug name and other details	Clinical symptoms and treatment methods	Mechanism and Risk factors
Medicines for diabetic disease: **- Drugs for diabetes** Sulfonylurea fast-acting insulin secretagogue α-glucosidase inhibitor Biguanide drugs Thiazolidine drug GLP-1 analog 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 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 Adrenalin 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 drug Quinidine sulfate hydrate, procainamide hydrochloride Class III antiarrhythmic drugs amiodarone hydrochloride, sotalol	QT prolongation might occur.	QT prolongation is seen with single administration of these drugs.

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 AUC 0-12hr of metformin

increased 20.9% due to co-administration).

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 C_{max} 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 C_{max} 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).

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 C_{max} 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 C_{max} 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 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 C_{max} 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).

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 C_{max} 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 hyperglycemia and may lead to loss of glycemic 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.

4.5 Fertility, Pregnancy and 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 extended release metformin in pregnant women. Hence, extended 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.

4.6 Effects on ability to drive and Use Machines

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.

4.5 Undesirable effects

Teneligliptin

The following adverse drug reactions have been identified in the clinical trials on Teneligliptin. In clinical trials conducted in Japan, 232 adverse reactions to this drug (including abnormal laboratory tests) were reported in 156 patients (9.5%) of total1645 patients. The most frequently observed adverse reactions were hypoglycemia in 43 patients (2.6%) and constipation in 14 patients (0.9%).

Patients with Inadequate Glycemic Control on Diet and Exercise Alone

In a clinical study conducted in 237 Indian patients with Type 2 Diabetes Mellitus inadequately controlled on diet and exercise alone. A total of 158 patients were exposed to Teneligliptin Tablets for a mean duration of 106.7 days. Adverse events considered to be related to study medication were reported for 6/158 (3.8%) of patients in the Teneligliptin group. The most frequent 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.

Significant adverse reactions:

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 biguanide: 1.1%, and in combination with α-glucosidase inhibitor: 1.3%). A severe hypoglycemia with loss of consciousness is noted when sulfonylurea co-administered with other DPP-4 inhibitors also and therefore, consider decreasing the quantity of sulfonylurea when co-administered

with teneligliptin. 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.

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.

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.

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/side effects:

If adverse reactions were observed then the drug administration should be discontinued and appropriate measures should be taken. *Table 5: 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 A LT (GPT), and increased γ-G TP	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 extended 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to the National Regulatory Authority.

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

Hypoglycemia 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 Actions

Ziten -M

Ziten -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 extended 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 degradation of GLP-1 by inhibiting dipeptidyl peptidase-4 (DPP-4) activity and thereby increasing blood concentration of active GLP-1

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 DPP-4 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.
t_{max}= Arithmetic mean value ± Standard Deviation

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 (C_{max}). 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 C_{max} and T_{max} 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 (T_{max}). 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 [^{14}C] 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 [^{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 AUC0-∞ of teneligliptin, M1, M2, M3, M4, and M5 with respect to AUC0-∞ 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 (IC 50 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.

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

Plasma concentration Teneligliptin

(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 on empty stomach to the healthyadults are shown below.

Table 1: 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
tmax= 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. The state of equilibrium will be attained within seven days

Table 2: Pharmacokinetic parameters at the time of repeated - dose oral drug administration in healthy adults

	C_{max} (ng/mL)	$AUC_{0\text{-}24hr}$ (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
tmax= 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 3: 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)

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 [^{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, 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.

Specific

Populations

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 Cmax and t1/2 of teneligliptin depending on the extent/degree of renal dysfunction. On the other hand, in the mild renal dysfunction patient (C_{cr} ≥50 to ≤ 80mL/min), moderate renal dysfunction patient (C_{cr} ≥30 to ≤50mL/min), and severe renal dysfunction patient (C_{cr}<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 hemodialysis.

Metformin

No pharmacokinetic studies of extended 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. Note that there was no clinical experience in high degree hepatic dysfunction patient (total score more than 9 by Child-Pugh classification).

Metformin

No pharmacokinetic studies of extended 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}, AUC0-∞,and t1/2 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

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Teneligliptin

Teneligliptin was non carcinogenic in rats and mice carcinogenicity

assays. In 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/m^2 basis] for neoplastic changes. In a 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/m^2 basis) for neoplastic changes.

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 showed 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 foetuses 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/m^2 basis), respectively for reproductive function,and early embryogenesis. Teneligliptin did not show 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/m^2 basis) was determined for embryo-fetal development in both rats and rabbits. In 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/m^2 basis).

Metformin

There are no such studies with extended 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 List of excipients

Microcrystalline
Cellulose (Avicel
PH 101) Maize
Starch
Ferric Oxide
Yellow
Purified Water
Hydroxy propyl
Cellulose
Hydroxy Propyl
Cellulose Colloidal

Silicon Dioxide
Magnesium Stearate
Guar Gum
(Luctoman P500)
Carboxy methyl
Cellulose Sodium
Methyl Paraben
Propyl Paraben
Hydroxy propyl Methyl Cellulose
Pregelatinized Starch (Starch
1500) Polyethylene Oxide (Polyox
WSR 301)
Hydrogenated Castor oil
Magnesium Stearate

6.2 Incompatibilities

Not Applicable.

6.3 Shelf life

24Months

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Aluminium Blister Pack

6.6 Special precautions for disposal and other handling

No special requirements.

7.0 MARKETING AUTHORISATION HOLDER

Glenmark Pharmaceuticals Ltd.

Registered office

Glenmark Pharmaceuticals Limited, B/2, Mahalaxmi Chambers, 22, Bhulabhai Desai road, Mumbai – 400 026, INDIA

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Manufacturing site

At: Village : Kishanpura , Baddi-Nalagarh Road, Tehsil Baddi, Distt Solan (H.P)-173205

8.0 MARKETING AUTHORISATION NUMBER(S)

MNB/05/182

9.0 DATE OF FIRST REGISTRATION/ RENEWAL OF THE MAH

10.0 DATE OF REVISION OF THE TEXT

24/March /2015