FOR THE USE ONLY OF A REGISTERED MEDICAL PRACTITIONER OR A HOSPITAL OR A LABORATORY

Rx Teneligliptin & Metformin Hydrochloride (Sustained Release)Tablets IP

Tenlifine® M 500 SR

टेनलीफाईन एम ५०० एसआर

COMPOSITION :

Each uncoated bilayered tablet contains :	
Teneligliptin Hydrobromide Hydrate Equivalent to Teneligliptin	20 mg
Metformin Hydrochloride IP	500 mg
(As sustained release)	
Excipients	q.s.
Colour : Ferric Oxide Yellow	

Tenlifine® M 1000 SR

टेनलीफाईन एम १००० एसआर

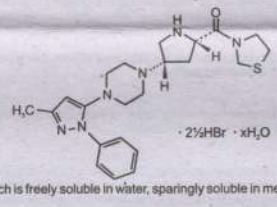
COMPOSITION :

Each uncoated bilayered tablet contains :	
Teneligliptin Hydrobromide Hydrate Equivalent to Teneligliptin	20 mg
Metformin Hydrochloride IP	1000 mg
(As sustained release)	
Excipients	q.s.
Colour : Ferric Oxide Yellow	

DESCRIPTION

Teneligliptin

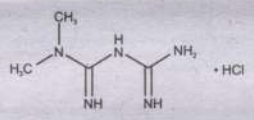
Teneligliptin is a DPP-4 inhibitor for the treatment of type-2 diabetes mellitus. Chemical name of Teneligliptin Hydrobromide Hydrate is {(2S, 4S) -4-[4- (3-Methyl-1-phenyl-1Hpyrazol-5-yl) piperazin-1-yl] pyrrolidin-2-yl}(1, 3-thiazolidin-3-yl) methanone hemipentahydrobromide hydrate and molecular formula is $C_{21}H_{30}N_6OS.$ 2½HBr.xH_2O. The molecular weight is 628.86 (anhydride) and structural formula is given below:



It is a white fine powder which is freely soluble in water, sparingly soluble in methanol, slightly soluble in ethanol (99.5), and insoluble in acetonitrile.

Metformin Hydrochloride

Metformin Hydrochloride (N, N-dimethylimidodicarbonimidic diamide hydrochloride) is a white to off-white crystalline compound with a molecular formula $C_4H_{11}N_5HCl$ and a molecular weight of 165.63. Metformin Hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4, The pH of 1% aqueous solution of Metformin Hydrochloride is 6.68, Metformin is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents The structural formula is as follows:



Metformin Hydrochloride

DOSAGE FORM

Tablets for oral use

INDICATION

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 is appropriate.

DOSAGE AND ADMINISTRATION

The usual adult dosage for oral use is one tablet once daily.

CLINICAL PHARMACOLOGY

1. Mechanism of action

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.

Metformin:

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects 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.

PHARMACOKINETICS:

Teneligliptin:

1. Plasma Concentration

a] *Single-dose Administration*

-	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng.hr/mL)	t_{max} (hr)	$t_{\frac{1}{2}}$ (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	3705.1 ± 787.0	1.0 (0.5-3.0)	20.8 ± 3.2

b] *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.

	C_{max}	$Auc_{0-\tau}$	T_{max}	$T_{\frac{1}{2}}$
Initial dose	160.60± 47.26	1627.9 ± 427.8	1.0 (0.4-2.0)	25.8 ± 4.9
After administration for 7 days.	220.14 ± 59.86	2641.4 ± 594.7	1.0 (1.0-1.0)	30.2 ± 6.9

c] *Influence of Meal to Drug Absorption*

Cmax decreased after a single dose of 20 mg of teneligliptin given post meal to the healthy adults as compared to empty stomach and tmax prolonged from 1.1 hr to 2.6 hr; however, no difference observed in AUC3).

	C_{max} (ng/mL)	AUC_{0-72hr} (ng.hr/mL)	$AUC_{0-\infty}$ (ng.hr/mL)	t_{max} (hr)	$t_{\frac{1}{2}}$ (hr)
Empty stomach	232.2 (236.2 ± 43.77)	1855.5 (1861.1 ± 148.1)	2090.3 (2094.8 ± 138.5)	1.1 ± 0.4	26.5 (27.8 ± 9.3)
Post meal	184.9 (187.5 ± 33.55)	1806.6 (1814.6 ± 183.3)	2044.0 (2056.1 ± 230.9)	2.6 ± 1.1	26.9 (28.3 ± 9.5)

2. Protein Binding Ratio

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.

3. Metabolism

(a) 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 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%.

(b) Mainly, CYP3A4 and flavin-containing monooxygenase (FMO1 and FMO3) participate in the metabolism of teneligliptin.

4. Excretion

When a single oral dose of 20 mg and 40 mg teneligliptin was given to the healthy adults on empty stomach, about 21.0 to 22.1% of dose was excreted as unaltered substance in urine, and the renal clearance was 37 to 39 mL/hr/kg.

5. Renal Dysfunction Patient

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 slight renal dysfunction patient (50≦ Ccr ≦ 80mL/min), moderate renal dysfunction patient (30≦ Ccr <50mL/min), and high renal dysfunction patient (Ccr <30mL/min), the AUC0-∞ was found to be about 1.25 times, 1.68 times, and 1.49 times, respectively, as compared to the healthy adults, and AUC0-43hr of terminal renal failure affected individual was about 1.16 times as compared to the healthy adults. Furthermore, 15.6% of teneligliptin dose was removed due to hemodialysis.

6. Hepatic Dysfunction Patients

When a single oral dose of 20 mg teneligliptin was given to the hepatic dysfunction patients, the Cmax of teneligliptin was found to be about 1.25 times and 1.38 times and AUC0-∞ was about 1.46 times and 1.59 times, respectively, in slight 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).

7. Pharmacokinetics in Elderly Patient

When a single oral dose of 20 mg teneligliptin was given to the healthy elderly patients (>=65 years old <=75 years old, 12 patients) and non-elderly patients (>=45 years old <=65 years old, 12 patents) on empty stomach, the ratio (90% confidence interval) of geometric minimum mean-square value of elderly patient with Cmax, 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:

1. Absorption and Bioavailability

The absolute bioavailability of a metformin hydrochloride 500 mg tablet given under fasting conditions is approximately 50-60%. Studies using single oral doses of metformin tablets of 500 mg and 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower mean peak concentration (C_{max}) and 25% lower area under the plasma concentration versus time curve(AUC), and a 35 minute prolongation of time to peak plasma concentration (Tmax) following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

2. Distribution

The apparent volume of distribution (V/F) of metformin following single oral doses of 850 mg averaged 654 + 358 L. Metformin is negligibly bound to plasma proteins in contrast to sulfonylureas which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin hydrochloride tablets, steady state plasma concentrations of metformin are reached within 24-48 hours and are generally c 1 pg/mL. During controlled clinical trials, maximum metformin plasma levels did not exceed 5 ug/mL, even at maximum doses.

3. Metabolism and Elimination

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) nor biliary excretion. Renal clearance is approximately 3.5 times greater than creatinine clearance which indicates that 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, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

4. Special Population

a. Patients with Type 2 Diabetes

In the presence of normal renal function, there are no differences between single or multiple dose pharmacokinetics of metformin between patients with type 2 diabetes and normal subjects, nor is there any accumulation of metformin in either group at usual clinical doses.

b. Renal Insufficiency

In subjects with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance.

c. Hepatic Insufficiency

No pharmacokinetic studies have been conducted in subjects with hepatic insufficiency.

d. Geriatrics

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 C max 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.

Metformin treatment should not be initiated in patients 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced.

e. Pediatric population

No data available in pediatric population.

Drug Interaction

Teneligliptin

Precautions for Co-administration

Drug Name	Clinical Condition/ Measures	Mechanism /Risk Factors
Drugs for diabetes Sulfonylurea fast-acting insulin secretagogue α-glucosidase inhibitor Biguanide drugs Thiazolidine drug GLP-1 analog preparation Insulin preparation	Since hypoglycemia might occur, these drugs should be administered while carefully observing the patient's condition. Particularly, when coadministered with sulfonylurea or insulin formulation, there is a possibility of higher risk of hypoglycemia. In order to reduce the risk of hypoglycemia caused by sulfonylurea or insulin formulation, consider decreasing the quantity of sulfonylurea or insulin formulation. When coadministered 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 hydrochloride	QT prolongation might occur.	QT prolongation is seen with single administration of these drugs.

(a) Coadministration with glimepiride

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, 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.

(b) Coadministration with pioglitazone

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 coadministration. 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 (24), 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.

(c) Coadministration with metformin

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.

(d) Coadministration with ketoconazole

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, 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 coadministration.

Effect on Electrocardiogram

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.

Metformin:

Glyburide - In a single-dose interaction study in type 2 diabetes subjects, co-administration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and C max were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects, makes the clinical significance of this interaction uncertain.

Furosemide - A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased the metformin plasma and blood Cmax by 22% and blood AUC by 15%, without any significant change in metformin renal clearance.

When administered with metformin, the Cmax and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when co-administered chronically.

Nifedipine – A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that co-administration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. 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, and 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, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of metformin and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Other - Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include thiazide 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 to maintain adequate glycemic control. In healthy volunteers, the pharmacokinetics of metformin and propranolol and metformin and ibuprofen were not affected when co-administered in single-dose interaction studies. Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

USE IN SPECIFIC POPULATIONS

Teneligliptin:

1. Use in the Elderly

In general, elderly patients often have physiological hypofunction; and therefore, these products should be administered carefully.

2. Use during Pregnancy, Delivery, or Lactation

This drug should be used in pregnant women or in women who may possibly be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment. (The safety of this 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.)

3. Pediatric Use

The safety of this product in low birth weight baby, newborn baby, infant, or little child has not been established.

4. Other Precautions

In overseas clinical trial, QT prolongation has been reported when 160 mg of this product was administered once daily.

Metformin:

1. Pregnancy

Teratogenic Effects: Pregnancy Category B.
Recent information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities. Most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible. Because animal reproduction studies are not always predictive of human response, metformin should not be used during pregnancy unless clearly needed. There are no adequate and well-controlled studies in pregnant women with metformin. Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about two and six times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

2. Nursing Mothers

Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted in nursing mothers. Because the potential for hypoglycemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Lf metformin is discontinued, and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

3. Geriatric Use

Controlled clinical studies of metformin hydrochloride tablets did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and younger patients. Metformin is known to be substantially excreted by the kidney and because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, it should only be used in patients with normal renal function. Because aging is associated with reduced renal function, metformin should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function Generally, elderly patients should not be titrated to the maximum dose of metformin.

CONTRAINDICATIONS

Teneligliptin:

(1) Patients having past history of hypersensitivity to ingredients of this product
(2) Patients having severe ketosis, diabetic coma or precoma, and type 1diabetes mellitus (since a prompt correction of hyperglycemia is required by transfusion and insulin, the administration of this product is not suitable)
(3) Patients having severe infection, perioperative, and severe external injury (since glycemic control is desired by insulin injection, the administration of this product is not suitable.)

Metformin:

1. Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels 2 I .5 mg/dL [males], 2 1.4 mg/dL [females] or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia.
2. Congestive heart failure requiring pharmacologic treatment.
3. Known hypersensitivity to metformin hydrochloride.
4. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

Metformin 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.

WARNINGS AND PRECAUTIONS

Teneligliptin:

A. Careful Administration

(1) Patient with higher degree of hepatic dysfunction (as there is no usage experience and safety has not been established.
(2) Patient with heart failure (NYHA class III–IV) (as there is no usage experience and safety has not been established.)
(3) Patient under sulfonylurea medication or insulin formulation (Risk of hypoglycemia may increase.
(4) Patients or conditions mentioned below (hypoglycemia might occur):

- Hypophyseoprivic or adrenal insufficiency
- Malnutrition, starved state, irregular dietary intake, insufficient dietary intake or hyposthenia
- Vigorous muscular movement
- Patient with excessive consumption of alcohol

(5) Patient with history of abdominal surgery or intestinal blockage (intestinal blockage might occur).
(6) Patient easily causing QT prolongation (such as patient having arrhythmia such as severe bradycardia or having its history, patient having heart disease such as congestive heart failure, and patient having hypokalemia (QT prolongation might occur).

B. Important Precautions

- The points regarding hypoglycemia and its coping strategy should be sufficiently explained to the patient when using this product. Particularly, when coadministered with sulfonylurea or insulin formulation, there is a possibility of higher risk of hypoglycemia. In order to reduce the risk of hypoglycemia caused by sulfonylurea or insulin formulation, consider decreasing the quantity these drugs when given in combination with sulfonylurea or insulin formulation.
- Consider its application only to the patient diagnosed with diabetes. In addition to diabetes, pay attention to diseases having symptoms (such as renal glycosuria, thyroid dysfunction) similar to diabetes, such as abnormal glucose tolerance/positive urine sugar.
- Consider the application of this product only when effect is insufficient after having sufficient diet and exercise therapy in advanced, which is a basic treatment for diabetes.
- During administration of this product, regularly check the blood sugar, check the effect of the drug, and in case, the drug effect is insufficient even after taking this product for 3 months, then change to other treatment.
- During continuous administration, there are cases that does not need medication, cases where quantity has to be reduced, and cases where there is no effect or insufficient effect due to complications of patient's intemperance and infections; and therefore, pay attention to dietary intake, blood sugar level, and presence of infections, as well as, always take care of selection of drugs, dosage, and whether to continue the drug.
- Since there is a possibility that adverse reactions, such as QT prolongation, might occur, it is desirable to avoid the medication in the patients having QT prolongation or its history (such as hereditary QT prolongation syndrome) or the patients having history of Torsades de pointes.
- Since there is a risk of hypoglycaemia, attention should be paid while administration of this drug to the patients engaged in car driving or working at high place.
- In regards to the coadministration of this drug and insulin formulation, the efficacy and the safety have not been studied.

Metformin:

Lactic Acidosis:

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with metformin; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is irriplicated as the cause of lactic acidosis, metformin plasma levels > 5 pg/mL are generally found.
Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 ml/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery.

Metformin-Precautions:

General

Monitoring of renal function - Metformin is known to be substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function, Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive metformin. In patients with advanced age, metformin should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging is associated with reduced renal function. In elderly patients, particularly those ≥ 80 years of age, renal function should be monitored regularly and, generally, metformin should not be titrated to the maximum dose.
Before initiation of metformin therapy and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and metformin discontinued if evidence of renal impairment is present.

Use of concomitant medications that may affect renal function or metformin disposition -

Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion, should be used with caution.

Radiologic studies involving the use of intravascular iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with contrast materials) –

Intravascular contrast studies with iodinated materials can leed 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, metformin should be 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 reevaluated and found to be normal.

Hypoxic states –

Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on metformin therapy, the drug should be promptly discontinued.

Surgical procedures –

Metformin therapy should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Alcohol intake –

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving metformin.

Impaired hepatic function –

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

Vitamin B12 levels –

A decrease to subnormal levels of previously normal serum vitamin B 12 levels, without clinical manifestations, is observed in approximately 7% of patients receiving metformin in controlled clinical trials of 29 weeks duration. Such decrease, possibly due to interference with B 12 absorption from the B 12 -intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin hydrochloride tablets or vitamin 812 supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on metformin 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 B 12 levels. In these patients, routine serum vitamin B 12 measurements at two- to three-year intervals may be useful.

Change in clinical status of patients with previous/y controlled type 2 diabetes –

A patient with type 2 diabetes previously well controlled on metformin hydrochloride tablets who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate and metformin levels. If acidosis of either form occurs, metformin must be stopped immediately and other appropriate corrective measures initiated.

Hypoglycemia –

Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but 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) or ethanol. Elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recbgnize in the elderly, and in people who are taking beta-adrenergic blocking drugs.

Loss of control of blood glucose –

When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold metformin and temporarily administer insulin. Metformin may be reinstituted after the acute episode is resolved. The effectiveness of oral antidiabetic drugs in lowering blood glucose to a targeted level decreases in many patients over a period of time. This phenomenon, which may be due to progression of the underlying disease or to diminished responsiveness to the drug, is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective during initial therapy. Should secondary failure occur with metformin or sulfonylurea monotherapy, combined therapy with metformin and sulfonylurea may result in a response. Should secondary failure occur with combined metformin/sulfonylurea therapy, it may be necessary to consider therapeutic alternatives including initiation of insulin therapy.

ADVERSE REACTIONS

Teneligliptin:

1) Hypoglycemia: Hypoglycemia may occur when coadministered with other drugs for diabetes (in case of glimepiride coadministration: 8.9% and in case of pioglitazone coadministration: 1.5%, in case of glinides drugs coadministration: 3.8%, in case of biguanide drugs coadministration: 1.1%, and in case of α-glucosidase inhibitor coadministration: 1.3%). Particularly, a severe hypoglycemia is observed when coadministered 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 coadministered with sulfonylurea. Furthermore, hypoglycemia (1.1%) is also reported when not coadministered with other drugs for diabetes. In case hypoglycemia is observed, appropriate measures must be taken such as intake of carbohydrate containing food.

2) Intestinal blockage (0.1%): Intestinal blockage 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.

3) Other Adverse Reactions:
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, increased AST (GOT), increased ALT (GPT), and increased γ-GTP, increase Al-P, albuminuria, positive ketone body, eczema, rash, pruritus, allergic dermatitis, increased CK (CPK), increased serum potassium, fatigue, allergic rhinitis, and increased serum uric acid.

Metformin:

1. Commonly observed adverse reactions:
Diarrhea
Nausea/Vomiting
Asthenia
Indigestion
Abdominal Discomfort
Headache

2. Other adverse reactions:
Abnormal stools, hypoglycemia, myalgia, lightheadedness, dyspnea, nail disorder, rash, sweating increased, taste disorder, chest discomfort, chills, flu syndrome, flushing, palpitation.

Direction: Swallow intact tablet. Do not break, crush or chew.

Storage : Store at temperature below 25°C. Away from direct sunlight heat & moisture.

Keep the medicine out of reach of children

PRESENTATION
Tenlifine-M 500 SR : Strip of 10 Tablets
Tenlifine-M 1000 SR : Strip of 10 Tablets

Mfg. Lic. No.: L/16/1795/MNB

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