For the use only of a Registered Medical Practitioners

Evogliptin Tablets 5 mg and Metformin Hydrochloride Sustained Release 1000 mg Tablets

VALERA M 1000

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1. Generic Name
Evogliptin Tablets 5 mg and Metformin Hydrochloride Sustained Release 1000 mg Tablets

2. Qualitative and quantitative composition
Each film-coated bilayered tablet contains:
Evogliptin Tartrate equivalent to
Evogliptin…………………………………..... 5 mg
Metformin Hydrochloride IP ………… 1000 mg
(As Sustained Release form)
Excipients……………………………..........q.s.
Colour: Ferric Oxide Red USP-NF (Red Oxide of Iron)

3. Dosage form and strength
Evogliptin and metformin combination is available for oral administration as tablets containing 5 mg evogliptin and 1000 mg metformin hydrochloride lease. The dose of FDC should be determined based on the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended daily dose of each ingredient, 5 mg evogliptin and 2,000 mg metformin. Generally, dose should be titrated gradually to reduce gastrointestinal side effects associated with metformin.

4. Clinical particulars
4.1 Therapeutic indication
As an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus who are appropriate for co-administration of evogliptin and metformin.
- Patients with inadequate glycemic control on metformin monotherapy
- Alternative for combination therapy of evogliptin and metformin

Important Limitations of Use: This FDC 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
<u>Posology</u>
Evogliptin and metformin combination is available for oral administration as tablets containing 5 mg evogliptin and 1000 mg metformin hydrochloride extended release. The dose of FDC should be determined based on the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended daily dose of each ingredient, 5 mg evogliptin and 2,000 mg metformin. Generally, dose should be titrated gradually to reduce gastrointestinal side effects associated with metformin. Evogliptin and metformin SR Tablet 5/1,000 mg should be taken as a single tablet once daily.
<u>Method of administration</u>
This FDC should be administered with food to reduce the gastrointestinal side effects associated with the metformin component. This FDC should be swallowed whole. The tablets must not be split, crushed, or chewed before swallowing
<u>Special Populations</u>
Pediatric Use: Safety and effectiveness of this FDC in paediatric 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 this FDC should have their renal function monitored regularly.
<u>Evogliptin:</u> There were 119 elderly patients (22.6%) aged 65 years or older out of a total of 527 patients in the phase II and III clinical studies of evogliptin. The administration in elderly patients has not been fully investigated. Since the elderly generally have decreased physiological functions such as hepatic and renal functions, caution needs to be exercised during administration while monitoring the patient's condition.

4.3 Contraindications
This FDC 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 septicaemia
• 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)

This FDC 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
<u>General</u>
This FDC should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.
<u>Pancreatitis</u>
Use of DPP4 inhibitors has been associated with a risk of developing acute pancreatitis. Patients should be informed of the characteristic symptoms of acute pancreatitis; persistent, severe abdominal pain. If pancreatitis is suspected, DPP4 inhibitors should be discontinued; if acute pancreatitis is confirmed, DPP4 inhibitors should not be restarted. Caution should be exercised in patients with a history of pancreatitis. There has been an isolated report of pancreatitis in a patient after administration of Evogliptin, however the causal association between
<u>Hypoglycaemia</u>
When co-administered with sulfonylurea or insulin formulation, there is a possibility of higher risk of hypoglycaemia. Therefore, caution is advised when this FDC 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 hypoglycaemia under usual circumstances of use, but hypoglycaemia 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. Heart failure: Caution should be exercised for patients with functional class I heart failure based on the New York Heart Association (NYHA) criteria as experience of administration is limited in such patients. Use of Evogliptin is not recommended to patients with functional class II-IV based on the NYHA criteria due to the absence of clinical experience in such patients.
<u>Lactic Acidosis</u>
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.
<u>Renal function</u>
The risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Therefore, This FDC 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. Evogliptin: It is confirmed that approximately 46.1% of the administered radioactivity was excreted in urine and approximately 42.8% in faces in healthy adults. This figure includes both the unchanged form and its metabolites. Since there is a concern that increased blood concentration of the unchanged form may persist in patients with moderate to severe renal impairment compared to patients with normal renal function, Evogliptin should be cautiously administered while monitoring the patient's condition. As there is no clinical experience of Evogliptin in patients with end-stage renal impairment requiring dialysis, administration of Evogliptin is not recommended in such patients.
<u>Impaired Hepatic Function</u>
Since impaired hepatic function has been associated with some cases of lactic acidosis, this FDC should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Hepatic impairment: Evogliptin: Dosage and administration adjustment is not needed in patients with mild to moderate hepatic impairment. No study was conducted in patients with severe hepatic impairment. Therefore, caution should be exercised in such patients.
<u>Vitamin B12 Levels</u>
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 parameter s on an annual basis is advised in patients on this FDC 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.
<u>Administration of iodinated contrast agent</u>
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, this FDC 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
<u>Hypoxic States</u>
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 this FDC therapy, the medication should be promptly discontinued.
<u>Surgery</u>
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.
<u>Use with Insulin</u>
The use of this FDC in combination with insulin has not been adequately studied.

4.5 Drugs interactions
Evogliptin:
1) Evogliptin is mainly metabolized by CYP3A4. In in vitro studies, evogliptin was not an inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4 enzymes or an inducer of CYP1A2, 2B6, and 3A4 enzymes. Thus, evogliptin is unlikely to cause interactions with other drugs acting as a substrate of such enzymes. Although evogliptin was proved to be a p-glycoprotein (P-gp) substrate and weak BCRP substrate based on in vitro studies, it did not inhibit transport mediated by these transporters. In addition, evogliptin was not a substrate of OAT1, OAT3, OCT2, OATP1B1, and OATP1B3 and did not inhibit them. Therefore, evogliptin is unlikely to cause interactions with drugs that act as a substrate of such transporters in the clinical dose.

2) Interaction of evogliptin with other drugs
• Metformin: Multiple administration of evogliptin 5 mg and twice daily metformin 1,000 mg (a substrate of OCT1 and OCT2) until steady state was reached did not show clinically meaningful change in the pharmacokinetics of evogliptin or metformin.
• Clarithromycin: Multiple administration of a potent CYP3A4 inhibitor, clarithromycin 1,000 mg/day, until steady state was reached and single administration of evogliptin 5 mg showed increased Cmax of evogliptin by 2.1 times and its AUC by 2.0 times. Caution needs to be exercised as pharmacokinetic exposure of evogliptin may increase with concomitant administration of CYP3A4 inhibitors.
• Rifampicin: Multiple administration of a potent CYP3A4 inducer, rifampicin 600 mg/day, until steady state was reached and single administration of evogliptin 5 mg showed no significant change in Cmax of evogliptin but showed a decrease in AUC by 63%.

3) Drug-Drug Interaction Study with Pioglitazone:
This study, in which Evogliptin 5 mg and Pioglitazone 30 mg were repeatedly administered individually or in combination with healthy volunteers to evaluate the drugs' pharmacokinetics, pharmacodynamics, tolerability and safety. For Evogliptin, the geometric mean ratio (GMR of E/(E + P)), and 90% confidence interval (CI) for Cmax,ss and AUCτ,ss after co-administration of Evogliptin and Pioglitazone (E+P), compared to the administration of Evogliptin alone, were 1.01 (0.97-1.05) and 1.01 (0.98- 1.04), respectively. For Pioglitazone, the geometric mean ratio (GMR of P/(E + P)) and 90% confidence interval (CI) for Cmax,ss and AUCτ,ss after co-administration of Evogliptin and Pioglitazone (E+P), compared to the administration of Pioglitazone alone, were 1.07 (0.99-1.17) and 1.08 (0.99–1.17), respectively.

4) Drug-Drug Interaction Study with Glimepiride:
This study in which Evogliptin 5 mg and Glimepiride 4 mg were repeatedly administered individually or in combination in healthy volunteers to evaluate pharmacokinetics, pharmacodynamics, tolerability, and safety of these drugs. For Evogliptin, the geometric mean ratio (GMR of (E+G)/E) and the 90% confidence interval (CI) for Cmax,ss and AUCτ,ss after co-administration of Evogliptin and Glimepiride (E+G) compared to administration of Evogliptin alone (E) were 1.02 (0.98 - 1.06) and 0.97 (0.95 – 1.00)), respectively. For Glimepiride, the geometric mean ratio (GMR of (E+G)/G)) and the 90% confidence interval (CI) for Cmax,ss and AUCτ,ss after co-administration of Evogliptin and Glimepiride (E+G) compared to administration of Glimepiride alone (G) were 1.08 (1.01 - 1.17) and 1.08 (1.02 – 1.14)), respectively.

5) Drug – drug interaction with Dapagliflozin:
Multiple administration of evogliptin 5 mg and dapagliflozin 10 mg (a substrate of UGT1A9) did not show clinically meaningful change in the pharmacokinetics of evogliptin or dapagliflozin

6) Drug – drug interaction with Empagliflozin:
Multiple administration of evogliptin 5 mg and empagliflozin 25 mg (a substrate of UGT2B7, UGT1A3, UGT1A8 and UGT1A9) did not show clinically meaningful change in the pharmacokinetics of evogliptin or empagliflozin.

<u>Metformin:</u>
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 in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)
<u>Evogliptin:</u>
Use in Pregnant women: No comparative study result is available in pregnant women. Results of animal studies showed that evogliptin was detected in the blood stream of fetus across the placenta up to 61.7% in pregnant rats and 14.1% in pregnant rabbits 2 hours after administration. Therefore, use in pregnant women is not recommended.
Use in Nursing Mothers: It is not evaluated whether evogliptin is excreted in human milk. Since animal studies confirmed that evogliptin is secreted in the milk, evogliptin should not be used in nursing mothers.
<u>Metformin:</u>
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.
Pediatric Use: Safety and effectiveness of this FDC in paediatric 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 this FDC should have their renal function monitored regularly.

4.7 Effects on ability to drive and use machines
<u>Evogliptin:</u>
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 Evogliptin is co-administered with sulphonylurea and/or insulin.
<u>Metformin:</u>
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
Evogliptin
1)Monotherapy
In the 12-week placebo-controlled monotherapy study using 2.5 mg, 5 mg, or 10 mg of evogliptin or placebo once daily, the adverse events reported with a frequency of 3% or higher are listed in Table 1.
Table 1. Adverse events reported in 3% or more patients in the 12-week placebo-controlled monotherapy study (regardless of investigator's causality assessment)

Adverse event	Evogliptin 2.5 mg N=39	Evogliptin 5 mg N=44	Evogliptin 10 mg N=38	Placebo N=36
Gastritis	2 (5.1%)	1 (2.3%)	0 (0.0%)	0 (0.0%)
Periodontitis	0 (0.0%)	0 (0.0%)	2 (5.3%)	0 (0.0%)
Nasopharyngitis	1 (2.6%)	4 (9.1%)	1 (2.6%)	1 (2.8%)
Erectile dysfunction	0 (0.0%)	0 (0.0%)	2 (5.3%)	0 (0.0%)

In the 24-week placebo-controlled monotherapy study using 5 mg of evogliptin or placebo once daily, the adverse events reported with a frequency of 3% or higher are listed in Table 2.
Table 2. Adverse events reported in 3% or more patients in the 24-week placebo-controlled monotherapy study (regardless of investigator's causality assessment)

Adverse event	Evogliptin 5 mg N=44	Placebo N=36
Dyspepsia	0 (0.0%)	0 (0.0%)
Nasopharyngitis	5 (6.4%)	0 (0.0%)
Arthralgia	3 (3.8%)	1 (2.8%)

In patients administering evogliptin 5 mg once daily as monotherapy for 52 weeks, the adverse events that occurred during the extension period (last 28 weeks) regardless of causality with increased frequency by 1% or higher compared to those of the 24-week study were toothache (3.1% vs. 1.3%) and contact dermatitis (3.1% vs. 1.3%). Compared to the 24-week study, there was no newly reported adverse event that occurred in two or more subjects (3.1%).
2)Combination therapy

In the 24-week active-drug-controlled combination therapy study with stable doses of metformin and either evogliptin 5 mg or Sitagliptin 100 mg once daily, the adverse events reported with a frequency of 3% or higher are listed in Table 3.

Table 3. Adverse events reported in 3% or more patients in the 24-week active-controlled combination therapy study (regardless of investigator's causality assessment)

Adverse event	Evogliptin 5 mg N=111	Sitagliptin 100 mg N=108
Dyspepsia	5 (4.5%)	3 (2.8%)
Diarrhoea	4 (3.6%)	1 (0.9%)
Nasopharyngitis	8 (7.2%)	9 (8.3%)
Pruritus	4 (3.6%)	1 (0.9%)

In the 52-week study using evogliptin 5 mg once daily combined with metformin, the adverse events that occurred during the extension period (last 28 weeks) regardless of causality with increased frequency by 1% or higher compared to those of the 24-week study were gastritis (2.2% vs. 0.9%) and upper respiratory tract infection (4.3% vs. 2.7%). Compared to the 24-week study, sciatica (2.2%) was a newly reported adverse event that occurred in two or more subjects (2.2%).

3)Hypoglycemia
In the 24-week monotherapy and combination therapy study with evogliptin 5 mg, hypoglycemia was each reported in one patient (monotherapy 1.3%, combination therapy 0.9%). All reported hypoglycemia cases were mild in severity and resolved without any action taken.
4)Vital signs
No clinically significant change in vital signs was observed in patients treated with Evogliptin.
Phase III clinical trial done by Alkem: A total of 38 (20.7%) patients reported 43 treatment emergent adverse events (TEAEs) during the study. No serious TEAEs were reported. No action was required (with IP or patient) for these 43 TEAEs. None of the TEAEs were severe or life threatening or fatal. No action was taken against study medication for all the 38/184 (20.7%) patients with 43 TEAEs. The study medication was neither interrupted nor discontinued for any patient. No patient was withdrawn from the study due to TEAEs. Majority of the TEAEs were mild in nature, dyslipidemia was most common, 6 events were reported in Evogliptin treatment group while 4 events were reported in Sitagliptin treatment group.
General Precautions:
1)Concomitant administration with drugs known to cause hypoglycemia: Insulin secretagogues such as insulin or sulfonylurea may cause hypoglycemia. Thus, lowering the dose of insulin or insulin secretagogues may be required to minimize the risk of hypoglycemia in case of concomitant administration with evogliptin. Severe and disabling joint pain
2)Severe and disabling joint pain has been reported in patients administering other DPP-4 inhibitors in post- marketing studies. The time to onset of symptoms following initiation of drug therapy varied from 1 day to years. Patients experienced relief of symptoms upon discontinuation of the medication. Some patients had a recurrence of severe joint pain when restarted on either their original DPP-4 inhibitor medication or another DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause of severe joint pain and discontinue evogliptin if appropriate.

<u>Metformin:</u>
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
<u>Evogliptin</u>
In clinical trials of evogliptin, single dose of evogliptin up to 60 mg daily was administered in healthy adults. In case of an overdose, perform symptomatic therapy (e.g., remove unabsorbed substance from the gastrointestinal tract, conduct clinical monitoring including electrocardiogram), and perform supportive therapy depending on the patient's condition.
<u>Metformin:</u>
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 Mechanism of Action
Evogliptin
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. Evogliptin 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
<u>Metformin:</u>
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

5.2Pharmacodynamic properties

This FDC tablets combine two antidiabetic medications with complementary mechanisms of action to improve glycemic control in adults with type 2 diabetes. Evogliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor, and metformin hydrochloride sustained release, is a member of the biguanide class.
Evogliptin in Combination with Metformin in Patients with Type II DM
The study was designed to evaluate the efficacy and safety of Evogliptin + metformin versus Sitagliptin + metformin in T2DM patients with inadequate glycemic control on metformin monotherapy. Following 24 weeks of treatment, the difference of change from baseline in the mean HbA1c (primary efficacy endpoint) between Evogliptin versus Sitagliptin was 0.06 with the upper limit of 0.22% for its 95% CI, which was lower than the pre-specified inferiority margin, 0.35%, demonstrating the non-inferiority of Evogliptin to Sitagliptin.
<u>Evogliptin:</u>
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. Evogliptin 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.
Mechanism of Action
The glucagon-like peptide-1 (GLP-1) is secreted from alimentary canal in response to meal that promotes insulin secretion from pancreas and regulates blood sugar post meal by controlling glucagon secretion. Evogliptin 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
In accordance with the results from biochemical studies, it was demonstrated that Evogliptin non-covalently binds to the catalytic site of human DPP4 enzyme in crystal structures complexed to human DPP4. ter-butoxy residue of Evogliptin distinictively interacts with Arg125 of human DPP4 unlike Sitagliptin and this hydrophobic interaction may contribute to the high binding affinity of Evogliptin.
Evogliptin is a competitive and reversible inhibitor of dipeptidyl peptidase IV (DPP-IV). The inhibitory activity of evogliptin is about 10-fold compared to Sitagliptin, also the selectivity of evogliptin for DPP-IV is 6,000-fold higher as compared to DPP8/9.
Pre-clinical studies on evogliptin demonstrated significant DPP-IV inhibitory activity, increased active plasma GLP1 level, reduced blood glucose excursion in a dose-dependent manner. By virtue of DPP-IV inhibitory effect, evogliptin exhibited significant improvement in the fasting and post-prandial blood glucose levels.

Comparisons of inhibitory potencies of Evogliptin and Sitagliptin against human plasma DPP4 activity

Compounds	Human Plasma DPP4 Inhibition	
	IC50	IC80
Evogliptin	3.0 ng/ml (7.5 nM)	6.8 ng/ml (16.9 nM)
Sitagliptin	13.9 ng/ml (34.1 nM)	46.3 ng/ml (113.7 nM)

Evogliptin is highly selective to DPP4 enzyme more than 6,000-fold against DPP4 closely-related enzymes, which was comparable or superior to those of Sitagliptin. Evogliptin is a selective DPP4 inhibitor and Evogliptin has little possibility of causing adverse events due to inhibition of DPP4 closely-related proteases.

The pharmacodynamic parameters of Evogliptin were also assessed in this Phase I study. The inhibition of DPP4 activity by Evogliptin, which is a primary pharmacodynamic evaluation parameter, was measured and calculated as the equation: (([Baseline DPP4 activity – DPP4 activity]*100)/ Baseline DPP4 activity). The time to reach maximum inhibition of DPP4 activity was generally consistent with the time to reach maximum plasma concentration of Evogliptin, Tmax of Evogliptin, which ranged from 2.5 to 5.5 hours. However, the maximum inhibition of DPP4 activity was reached before Tmax of Evogliptin in 40 mg and 60 mg dose groups. The maximum degree of inhibition showed a dose-dependent increase, reaching highest 97.1% inhibition from baseline at a dose of 60 mg. The dose groups of 10 mg and higher showed more than 80% inhibition of DPP4 activity, and this inhibition was sustained over a 24-hour period. The duration of DPP4 inhibition for more than 80% inhibition increased in a dose-dependent manner.

Evogliptin Monotherapy in Patients with Type II DM
The study was designed to evaluate the efficacy and safety of Evogliptin 5 mg oral dose and determine the optimal dose and regimen in T2DM patients with inadequate glycemic control on exercise and diet.
The difference of changes in HbA1c (primary efficacy endpoint) between Evogliptin versus placebo from baseline to 24 weeks of treatment was -0.28%, which was statistically significant (p<0.0001).

<u>Metformin:</u>
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.

5.3 Pharmacokinetic properties
<u>Evogliptin:</u>
The maximum Evogliptin concentrations (Cmax) were observed at 3.0 to 5.5 hours (median value), and the average half-lives (t1/2) were estimated to be 32.5 to 39.8 hours. The average Cmax and AUClast values increased as the dose increased while dose-dependent changes were not shown in Tmax and t1/2.
Multiple ascending dose (MAD) study: The maximum Evogliptin concentrations (Cmax) were observed at 4.0 to 5.0 hours (median value) after the last administration of Evogliptin at 5, 10, and 20 mg (Day 10), and the average half-lives (t1/2) were estimated to be 32.9 to 38.8 hours. Dose-dependent changes were not shown in Tmax and t1/2 while the average Cmax,ss and AUC216-249h,ss values increased as the doses increased. The accumulation ratios were 1.44, 1.38 and 1.50 at 5, 10, and 20 mg of Evogliptin, respectively.
The absolute bioavailability of Evogliptin was 50.247%. Plasma protein binding of Evogliptin is 46%.
In in vitro and in vivo metabolism study of Evogliptin in rat, dog, monkey, and human liver microsome, total seventeen kinds of metabolites were identified. Among them, M7 and M8 (mono-hydroxylated metabolites), and M16 (glucuronide metabolite) were major metabolites. CYP3A4 plays the major role in hydroxylation of Evogliptin to M7 and M8, and UGT2B7 plays the major role in the glucuronidation of M7 to M16.
In CYP inhibition assay in human liver microsome using in vitro cocktail of probe substrates, Evogliptin up to 50 μM did not show significant inhibition against activities of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4, suggesting the negligible CYP inhibition activity of the drug. In addition, it was found that Evogliptin has negligible potential of CYP1A2, 2B6 and 3A4 induction in cryopreserved human hepatocytes. Evogliptin was found to be a substrate of P-gp, but not a substrate of BCRP, OAT1B1, OAT1B3, OAT1, OAT3, or OCT2, and not an inhibitor of any of these transporters.
Renal Impairment: In study cohorts classified using the MDRD eGFR, the geometric means ratio (90% CIs) of Cmax and AUClast were 1.52 (1.22 - 1.89) and 1.98 (1.59 - 2.46) for those with severe renal impairment versus healthy volunteers and 1.32 (1.08 – 1.61) and 1.8 (1.47 – 2.21) for those with moderate renal impairment versus healthy volunteers, respectively. In contrast, patients with mild renal impairment showed the PD parameters comparable to healthy volunteers; the corresponding geometric means ratio (90% CIs) of Cmax and AUClast were 1.04 (0.85 - 1.27) and 1.2 (0.98 - 1.47).
<u>Metformin:</u>
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. 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. 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. 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. 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. No pharmacokinetic studies of sustained release metformin have been conducted in subjects with hepatic insufficiency. 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.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology
The toxicity of Evogliptin has been characterized in single and repeated oral dosing toxicity studies in mice, rats and dogs. Safety pharmacology studies and genotoxicity assessments have been also conducted. Carcinogenicity studies for 104 weeks in rats and dogs are on-going. In the acute toxicity study in rats, the lethal dose of Evogliptin was observed to be above 2,000 mg/kg. In the repeated dosing studies in mice, rats, and dogs, the no-observed-adverse-effect-level (NOAEL) was determined to be 300 mg/kg/day, 300 mg/kg/day, and 200 mg/kg/day, respectively. In the study of bacterial reverse mutation, Evogliptin showed a negative response. Evogliptin did not induce chromosomal aberrations in cultured CHL cells. In vivo micronucleus test in bone marrow cells of ICR mice showed that Evogliptin did not induce an increased frequency of micronuclei in the bone marrow cells of ICR mice. In safety pharmacology studies, it was confirmed that Evogliptin did not affect central nervous system and respiratory system after oral administration in rats, up to dose of 300 mg/kg. In a dog telemetry study, increase of heart rate, vomiting, and several changes of ECG parameter were observed at a high dose (300 mg/kg). But, there were no effects on blood pressure and body temperature even at the high dose (300 mg/kg). In hERG channel assay, an IC50 value of Evogliptin was approximately 143.4 μM. In consideration of Cmax at 5 mg administration in humans, this IC50 value represents an enough safety margin over 10,000 times. Pre-clinical studies revealed no carcinogenicity, mutagenicity and/or fertility impairment. Evogliptin showed no drug-related tumors in either sex of mice or rats upto the highest dose of 100 mg/kg/day (>25-fold or >80- fold higher exposure than in humans, respectively) for a period of two years.
<u>Metformin:</u>
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.

7. Description
Film-coated bilayer tablet. Blister strip of 15 tablets.

8. Pharmaceutical particulars

8.1 Incompatibilities
Not applicable

8.2 Shelf-life
24 months from the date of manufacturing.

8.3 Packaging information
Blister strip of 15 tablets.

8.4 Storage and handling instructions
Store at a temperature not exceeding 30C, protected from light and moisture.

9. Patient Counselling Information
Patients should be informed of the potential risks and benefits of Valera M 1000/500 and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and A1C testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications. During periods of stress such as fever, trauma, infection, or surgery, medication requirements may change and patients should be advised to seek medical advice promptly. The risks of lactic acidosis due to the metformin component, its symptoms, and conditions that predispose to its development, as noted in Warnings and Precautions, should be explained to patients. Patients should be advised to discontinue Valera M 1000/500 immediately and to promptly notify their health practitioner if unexplained hyperventilation, myalgia, malaise, unusual somnolence, dizziness, slow or irregular heart beat, sensation of feeling cold (especially in the extremities) or other nonspecific symptoms occur. Gastrointestinal symptoms are common during initiation of metformin treatment and may occur during initiation of Valera M 1000/500 therapy; however, patients should consult their physician if they develop unexplained symptoms. Although gastrointestinal symptoms that occur after stabilization are unlikely to be drug related, such an occurrence of symptoms should be evaluated to determine if it may be due to lactic acidosis or other serious disease. Patients should be counseled against excessive alcohol intake, either acute or chronic, while receiving Valera M 1000/500. Patients should be informed about the importance of regular testing of renal function and hematological parameters when receiving treatment with Valera M 1000/500. Patients should be informed that acute pancreatitis has been reported during postmarketing use of Valera M 1000/500. Patients should be informed that persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Patients should be instructed to promptly discontinue Valera M 1000/500 and contact their physician if persistent severe abdominal pain occurs. Patients should be informed that the incidence of hypoglycemia is increased when Valera M 1000/500 is added to an insulin secretagogue (e.g., sulfonylurea) or insulin therapy and that a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia. Patients should be informed that allergic reactions have been reported during postmarketing use of Evogliptin, one of the components of Valera M 1000/500. If symptoms of allergic reactions (including rash, hives, and swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing) occur, patients must stop taking Valera M 1000/500 and seek medical advice promptly.
Physicians should instruct their patients to read the Medication Guide before starting Valera M 1000/500 therapy and to reread each time the prescription is renewed. Patients should be instructed to inform their doctor if they develop any bothersome or unusual symptom, or if any symptom persists or worsens.
Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet.

10. Details of manufacturer:

Made in India by:
ALKEM HEALTH SCIENCE
A Unit of Alkem Laboratories Limited, Unit-2,
Samardung, Karek Block,
P.O. Namthang, South Sikkim-737 137.

Marketed by:
ALKEM LABORATORIES LTD.
ALKEM HOUSE, Senapati Bapat Marg,
Lower Parel, Mumbai - 400 013.
To report a product query & adverse drug
event, please reach us at-pvglobal@alkem.com

11. Details of permission or licence number with date
Mfg. Licence No. M/756/2016 dated 24/01/2017 validity 31/12/2021.

12. Date of Revision:
04/12/2020