GENIX

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Trade Name: Gvia-M 50mg/1000 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION PER BATCH

Composition (APIs):
Each film-coated tablet contains:
Sitagliptin phosphate ·····50mg
Metformin HCl·····1000mg

BATCH FORMULA:
Batch size: 400,000 Tablets

S.No	Name of Raw material	Role in formulation	Specification	Unit/dose (mg/tab)
1	Sitagliptin Phopshate	API	USP	64.25
2	Metformin Hydrochloride	API	USP	1000
3	Povidone (PVP K-30)	Binder	USP	25.750
4	Hypromellose (Pharmacoat 606)	Binder		15.00
5	Sodium Lauryl Sulphate	Surfactant	USP	5.0
6	Magnesium Stearate	Glidant	USP	20.00
COATING				
7	Hypromellose (Pharmacoat 606)	Coating agent	USP	12.00
8	Talc	Glidant	BP	6.0
9	Titanium dioxide	Pigment/Opacifier	USP	3.750
10	Polyethylene glycol 6000, flakes	Polishing agent	USP	6.0
11	Povidone (PVP-K)	Binder	USP	5.750
12	Dye, Yellow Sicopharm	Coloring agent	In-House	0.04

3. PHARMACEUTICAL FORM

Film-coated tablet.

Oblong, Green, Biconvex, film coated tablets Engraved “GENIX” on one side and “Score line” on other side

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Gvia-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 sitagliptin and metformin is appropriate. Important Limitations of Use
Gvia-M should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

Gvia-M has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using Gvia-M.

4.2 Posology and method of administration

Posology:

Recommended Dosing

The dosage of GVIA-M should be individualized on the basis of the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended daily dose of 100 mg sitagliptin and 2000 mg metformin. Initial combination therapy or maintenance of combination therapy should be individualized and left to the discretion of the health care provider.

GVIA-M should generally be given twice daily with meals, with gradual dose escalation, to reduce the gastrointestinal (GI) side effects due to metformin. GVIA-M must not be split or divided before swallowing.

The starting dose of GVIA-M should be based on the patient's current regimen. GVIA-M should be given twice daily with meals. The following doses are available:
50 mg sitagliptin/500 mg metformin hydrochloride50 mg sitagliptin/1000 mg metformin hydrochloride.

The recommended starting dose in patients not currently treated with metformin is 50 mg sitagliptin/500 mg metformin hydrochloride twice daily, with gradual dose escalation recommended to reduce gastrointestinal side effects associated with metformin.
The starting dose in patients already treated with metformin should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and the dose of metformin already being taken. For patients taking metformin 850 mg twice daily, the recommended starting dose of GVIA-M is 50 mg sitagliptin/1000 mg metformin hydrochloride twice daily.

Patients treated with an insulin secretagogue or insulin.
Co-administration of GVIA-M with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower doses of the insulin secretagogue or insulin to reduce the risk of hypoglycemia. No studies have been performed specifically examining the safety and efficacy of GVIA-M in patients previously treated with other oral antihyperglycemic agents and switched to GVIA-M. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring as changes in glycemic control can occur.

4.3 Contraindications

GVIA-M (sitagliptin/metformin HCl) is contraindicated in patients with:
• Renal impairment (e.g., serum creatinine levels greater than or equal to 1.5 mg/dL for men, greater than or equal to 1.4 mg/dL for women or abnormal creatinine clearance), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia .
•Hypersensitivity to metformin hydrochloride.
•Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.
•History of a serious hypersensitivity reaction to GVIA-M or sitagliptin (one of the components of GVIAM), such as anaphylaxis or angioedema.

4.4 Special warnings and precautions for use
Lactic Acidosis
Metformin hydrochloride
Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with GVIA-M; 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. W hen metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 μg/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (Approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal impairment, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin and by use of the minimum effective dose of metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis.
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. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking metformin, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure.
The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur.
Metformin should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose, and if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of metformin, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.
Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking metformin do not necessarily indicate impending lactic acidosis

and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling [see Warnings and Precautions (5.8, 5.13)]. Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).
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.

Pancreatitis
There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or Necrotizing pancreatitis, in patients taking GVIA-M. After initiation of GVIA-M, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, GVIA-M should promptly be discontinued and appropriate management should be initiated. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using GVIA-M.

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

Assessment of Renal Function
Metformin and sitagliptin are known to be substantially excreted by the kidney.

Metformin hydrochloride
The risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Therefore, GVIA-M is contraindicated in patients with renal impairment. Before initiation ofGVIA-M and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated (e.g., elderly), renal function should be assessed more frequently and GVIA-M discontinued if evidence of renal impairment is present.

Sitagliptin
There have been postmarketing reports of worsening renal function, including acute renal failure, sometimes requiring dialysis. Before initiation of therapy with GVIA-M and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, particularly in elderly patients, renal function should be assessed more frequently and GVIA-M discontinued if evidence of renal impairment is present.

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 anemia 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 GVIA-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.

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 GVIA-M.

Surgical Procedures
Use of GVIA-M 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.

Change in Clinical Status of Patients with Previously Controlled Type 2 Diabetes
A patient with type 2 diabetes previously well controlled on GVIA-M 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, GVIA-M must be stopped immediately and other appropriate corrective measures initiated.

Use with Medications Known to Cause Hypoglycemia
Sitagliptin
When sitagliptin was used in combination with a sulfonylurea or with insulin, medications known to cause hypoglycemia, the incidence of hypoglycemia was increased over that of placebo used in Combination with a sulfonylurea or with insulin. Therefore, patients also receiving an insulin secretagogue (e.g., sulfonylurea) or insulin may require a lower dose of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.

Metformin hydrochloride
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 and insulin) 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 recognize in the elderly, and in people who are taking β-adrenergic blocking drugs.

Surgical Procedures
Use of GVIA-M 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.

Change in Clinical Status of Patients with Previously Controlled Type 2 Diabetes
A patient with type 2 diabetes previously well controlled on GVIA-M 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, GVIA-M must be stopped immediately and other appropriate corrective measures initiated.

Use with Medications Known to Cause Hypoglycemia
Sitagliptin
When sitagliptin was used in combination with a sulfonylurea or with insulin, medications known to cause hypoglycemia, the incidence of hypoglycemia was increased over that of placebo used in combination with a sulfonylurea or with insulin [see Adverse Reactions (6)]. Therefore, patients also receiving an insulin secretagogue (e.g., sulfonylurea) or insulin may require a lower dose of the insulin secretagogue or insulin to reduce the risk of hypoglycemia

Metformin hydrochloride
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 andinsulin) 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 recognize in the elderly, and in people who are taking β-adrenergic blocking drugs. Angioedema has also been reported with other dipeptidyl peptidase-4 (DPP-4) inhibitors. Use caution in a patient with a history of angioedema with another DPP-4 inhibitor because it is unknown whether such patients will be
predisposed to angioedema with GVIA-M.

Macrovascular Outcomes
There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with GVIA-M or any other anti-diabetic drug.

4.5 Interaction with other medicinal products and other forms of interaction
Carbonic Anhydrase Inhibitors
Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently decrease serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis.

Concomitant use of these drugs may induce metabolic acidosis. Use these drugs with caution in patients treated with GVIA-M, as the risk of lactic acidosis may increase.

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.

Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of GVIA-M and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

The Use of Metformin with Other Drugs
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 GVIA-M the patient should be closely observed to maintain adequate glycemic control.

4.6 Pregnancy and lactation

Pregnancy
There are no adequate data from the use of sitagliptin in pregnant women. Studies in animals have shown reproductive toxicity at high doses of sitagliptin.
A limited amount of data suggest the use of metformin in pregnant women is not associated with an increased risk of congenital malformations. Animal studies with metformin do not indicate harmful effects with respect to pregnancy, embryonic or foetal development, parturition or postnatal development.
Gvia-M should not be used during pregnancy. If a patient wishes to become pregnant or if a pregnancy occurs, treatment with Gvia-M should be discontinued and switched to insulin treatment as soon as possible.

Breast-feeding
No studies in lactating animals have been conducted with the combined active substances of Gvia-M. In studies performed with the individual active substances, both sitagliptin and metformin are excreted in the milk of lactating rats. Metformin is excreted in human milk in small amounts. It is not known whether sitagliptin is excreted in human milk. Gvia-M must therefore not be used in women who are breastfeeding.

Fertility
Animal data do not suggest an effect of treatment with sitagliptin on male and female fertility. Human data are lacking.

4.7 Effects on ability to drive and use machines
Gvia-M has no or negligible influence on the ability to drive and use machines. However, when driving or using machines, it should be taken into account that dizziness and somnolence have been reported with sitagliptin.

In addition, patients should be alerted to the risk of hypoglycaemia when Gvia-M is used in combination with a sulphonyl urea or with insulin.

4.8 Overdose:

During controlled clinical trials in healthy subjects, single doses of up to 800 mg sitagliptin were generally well tolerated. Minimal increases in QTc, not considered to be clinically relevant, were observed in one study at a dose of 800 mg sitagliptin. There is no experience with doses above 800 mg in clinical studies.

In Phase I multiple-dose studies, there were no dose-related clinical adverse reactions observed with sitagliptin with doses of up to 600 mg per day for periods of up to 10 days and 400 mg per day for periods of up to 28 days.

A large overdose of metformin (or co-existing risks of lactic acidosis) may lead to lactic acidosis which is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis.
In clinical studies, approximately 13.5 % of the dose was removed over a 3- to 4-hour haemodialysis session. Prolonged haemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialysable by peritoneal dialysis.
In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastro-intestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy if required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
Drugs used in diabetes, Combinations of oral blood glucose lowering drugs, ATC code: A10BD07
Gvia-M combines two antihyperglycaemic medicinal products with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: sitagliptin phosphate, a dipeptidyl peptidase 4 (DPP-4) inhibitor, and metformin hydrochloride, a member of the biguanide class.

Sitagliptin

Mechanism of action
Sitagliptin phosphate is an orally-active, potent, and highly selective inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzyme for the treatment of type 2 diabetes. The DPP-4 inhibitors are a class of agents that act as incretin enhancers. By inhibiting the DPP-4 enzyme, sitagliptin increases the levels of two known active incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells. GLP-1 also lowers glucagon secretion from pancreatic
alpha cells, leading to reduced hepatic glucose production. When blood glucose levels are low, insulin release is not enhanced and glucagon secretion is not suppressed. Sitagliptin is a potent and highly selective inhibitor of the enzyme DPP-4 and does not inhibit the closely-related enzymes DPP-8 or DPP- 9 at therapeutic concentrations. Sitagliptin differs in chemical structure and pharmacological action from GLP-1 analogues, insulin, sulphonylureas or meglitinides, biguanides, peroxisome proliferator-activated receptor gamma (PPARγ) agonists, alpha-glucosidase inhibitors, and amylin analogues.
In a two-day study in healthy subjects, sitagliptin alone increased active GLP-1 concentrations, whereas metformin alone increased active and total GLP-1 concentrations to similar extents. Co-administration of sitagliptin and metformin had an additive effect on

active GLP-1 concentrations. Sitagliptin, but not metformin, increased active GIP concentrations.

Clinical efficacy and safety
Overall, sitagliptin improved glycaemic control when used as monotherapy or in combination treatment. In clinical trials, sitagliptin as monotherapy improved glycaemic control with significant reductions in haemoglobin A_{1c}(HbA_{1c}) and fasting and postprandial glucose. Reduction in fasting plasma glucose (FPG) was observed at three weeks, the first time point at which FPG was measured. The observed incidence of hypoglycaemia in patients treated with sitagliptin was similar to placebo. Body weight did not increase from baseline with sitagliptin therapy. Improvements in surrogate markers of beta cell function, including HOMA-β (Homeostasis Model Assessment-β), proinsulin to insulin ratio, and measures of beta cell responsiveness from the frequently-sampled meal tolerance test were observed.

Studies of sitagliptin in combination with metformin
In a 24-week, placebo-controlled clinical study to evaluate the efficacy and safety of the addition of sitagliptin 100 mg once daily to ongoing metformin, sitagliptin provided significant improvements in glycaemic parameters compared with placebo. Change from baseline in body weight was similar for patients treated with sitagliptin relative to placebo. In this study there was a similar incidence of hypoglycaemia reported for patients treated with sitagliptin or placebo.
In a 24-week placebo-controlled factorial study of initial therapy, sitagliptin 50 mg twice daily in combination with metformin (500 mg or 1,000 mg twice daily) provided significant improvements in glycaemic parameters compared with either monotherapy. The decrease in body weight with the combination of sitagliptin and metformin was similar to that observed with metformin alone or placebo; there was no change from baseline for patients on sitagliptin alone. The incidence of hypoglycaemia was
similar across treatment groups.

Study of sitagliptin in combination with metformin and a sulphonylurea
A 24-week placebo-controlled study was designed to evaluate the efficacy and safety of sitagliptin (100 mg once daily) added to glimepiride (alone or in combination with metformin). The addition of sitagliptin to glimepiride and metformin provided significant improvements in glycaemic parameters. Patients treated with sitagliptin had a modest increase in body weight (+1.1 kg) compared to those given placebo.

Study of sitagliptin in combination with metformin and a PPARγ agonist
A 26-week placebo-controlled study was designed to evaluate the efficacy and safety of sitagliptin (100 mg once daily) added to the combination of pioglitazone and metformin. The addition of sitagliptin to pioglitazone and metformin provided significant improvements in glycaemic parameters. Change from baseline in body weight was similar for patients treated with sitagliptin relative to placebo. The incidence of hypoglycaemia was also similar in patients treated with sitagliptin or placebo.

Study of sitagliptin in combination with metformin and insulin
A 24-week placebo-controlled study was designed to evaluate the efficacy and safety of sitagliptin (100mg once daily) added to insulin (at a stable dose for at least 10 weeks) with or without metformin (at least 1,500 mg). In patients taking pre-mixed insulin, the mean daily dose was 70.9 U/day. In patients taking non-pre-mixed (intermediate/long-acting) insulin, the mean daily dose was 44.3 U/day. Data from the 73 % of patients who were taking metformin

are presented in Table 3. The addition of sitagliptin to insulin provided significant improvements in glycaemic parameters. There was no meaningful change from baseline in body weight in either group.

Table 3: HbA_{1c} results in placebo-controlled combination therapy studies of sitagliptin and metformin*

Study	Mean baseline HbA_{1c} (%)	Mean change from baseline HbA_{1c} (%)	Placebo-corrected mean change in HbA_{1c} (%) (95 % CI)
Sitagliptin 100 mg once daily added to ongoing metformin therapy[%] (N=453)	8.0	-0.7[†]	-0.7[†,‡] (-0.8, -0.5)
Sitagliptin 100 mg once daily added to ongoing glimepiride + metformin therapy[%] (N=115)	8.3	-0.6[†]	-0.9[†,‡] (-1.1, -0.7)
Sitagliptin 100 mg once daily added to ongoing pioglitazone + metformin therapy[¶] (N=152)	8.8	-1.2[†]	-0.7[†,‡] (-1.0, -0.5)
Sitagliptin 100 mg once daily added to ongoing insulin + metformin therapy [%] (N=223)	8.7	-0.7[§]	-0.5[§,‡] (-0.7, -0.4)
Initial Therapy (twice daily)[%]: Sitagliptin 50 mg + metformin 500 mg (N=183)	8.8	-1.4[†]	-1.6[†,‡] (-1.8, -1.3)
Initial Therapy (twice daily)[%]: Sitagliptin 50 mg + metformin 1,000 mg (N=178)	8.8	-1.9[†]	-2.1[†,‡] (-2.3, -1.8)

* All Patients Treated Population (an intention-to-treat analysis).
[†] Least squares means adjusted for prior antihyperglycaemic therapy status and baseline value.
[‡] $p < 0.001$ compared to placebo or placebo + combination treatment.
[%] HbA_{1c} (%) at week 24.
[¶] HbA_{1c} (%) at week 26
[§] Least squares mean adjusted for insulin use at Visit 1 (pre-mixed vs. non-pre-mixed [intermediate- or long-acting]), and baseline value.

In a 52-week study, comparing the efficacy and safety of the addition of sitagliptin 100 mg once daily or glipizide (a sulphonylurea) in patients with inadequate glycaemic control on metformin monotherapy, sitagliptin was similar to glipizide in reducing HbA_{1c} (-0.7 % mean change from baselines at week 52, with baseline HbA_{1c} of approximately 7.5 % in both groups). The mean glipizide dose used in the comparator group was 10 mg per day with approximately 40 % of patients requiring a glipizide dose of ≤ 5 mg/day throughout the study. However, more patients in the sitagliptin group discontinued due to lack of efficacy than in the glipizide group. Patients treated with sitagliptin exhibited a significant mean decrease from baseline in body weight (-1.5 kg) compared to a significant weight gain in patients administered glipizide (+1.1 kg). In this study, the proinsulin to insulin ratio, a marker of efficiency of insulin synthesis and release, improved with sitagliptin and deteriorated with glipizide treatment. The incidence of hypoglycaemia in the sitagliptin group (4.9 %) was significantly lower than that in the glipizide group (32.0 %).

A 24 week placebo-controlled study involving 660 patients was designed to evaluate the insulin-sparing efficacy and safety of sitagliptin (100 mg once daily) added to insulin glargine with or without metformin (at least 1,500 mg) during intensification of insulin therapy. Among patients taking metformin, baseline HbA_{1c} was 8.70 % and baseline insulin dose was 37 IU/day. Patients were instructed to titrate their insulin glargine dose based on fingerstick fasting glucose values. Among patients taking metformin, at Week 24, the increase in daily insulin dose was 19 IU/day in patients treated with sitagliptin and 24 IU/day in patients treated with placebo. The reduction in HbA_{1c} for patients treated with sitagliptin, metformin, and insulin was -1.35 % compared to -0.90 % for patients treated with placebo, metformin, and insulin, a difference of -0.45 % [95 % CI: -0.62, -0.29]. The incidence of hypoglycaemia was 24.9 % for patients treated with sitagliptin, metformin, and insulin and 37.8 % for patients treated with placebo, metformin, and insulin. The difference was mainly due to a higher percentage of patients in the placebo group experiencing 3 or more episodes of hypoglycaemia (9.4 vs. 19.2 %). There was no difference in the incidence of severe hypoglycaemia.

Metformin

Mechanism of action

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via three mechanisms:

- by reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
- in muscle, by modestly increasing insulin sensitivity, improving peripheral glucose uptake and utilisation
- by delaying intestinal glucose absorption

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of specific types of membrane glucose transporters (GLUT-1 and GLUT-4).

Clinical efficacy and safety

In humans, independently of its action on glycaemia, metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin reduces total cholesterol, LDLc and triglyceride levels.

The prospective randomised (UKPDS) study has established the long-term benefit of intensive blood glucose control in type 2 diabetes. Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

- a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/1,000 patient-years) versus diet alone (43.3 events/1,000 patient-years), p=0.0023, and versus the combined sulphonylurea and insulin monotherapy groups (40.1 events/1,000 patient-years), p=0.0034
- a significant reduction of the absolute risk of any diabetes-related mortality: metformin 7.5 events/1,000 patient-years, diet alone 12.7 events/1,000 patient-years, p=0.017
- a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/1,000 patient-years versus diet alone 20.6 events/1,000 patient-years, (p=0.011), and versus the combined sulphonylurea and insulin monotherapy groups 18.9 events/1,000 patient-years (p=0.021)
- a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/1,000 patient-years, diet alone 18 events/1,000 patient-years, (p=0.01).

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Gvia-M in all subsets of the paediatric population in type 2 diabetes mellitus.

5.2 Pharmacokinetic properties

A bioequivalence study in healthy subjects demonstrated that the Gvia-M (sitagliptin/metformin hydrochloride) combination tablets are bioequivalent to co-administration of sitagliptin phosphate and metformin hydrochloride as individual tablets.

Sitagliptin

Absorption

Following oral administration of a 100-mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median T_{max}) occurring 1 to 4 hours post-dose, mean plasma AUC of sitagliptin was 8.52 μM•hr, C_{max} was 950 nM. The absolute bioavailability of sitagliptin is approximately 87 %. Since co-administration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics, sitagliptin may be administered with or without food.
Plasma AUC of sitagliptin increased in a dose-proportional manner. Dose-proportionality was not established for C_{max} and C_{24hr} (C_{max} increased in a greater than dose-proportional manner and C_{24hr} increased in a less than dose-proportional manner).

Distribution

The mean volume of distribution at steady state following a single 100-mg intravenous dose of sitagliptin to healthy subjects is approximately 198 litres. The fraction of sitagliptin reversibly bound to plasma proteins is low (38 %).

Biotransformation

Sitagliptin is primarily eliminated unchanged in urine, and metabolism is a minor pathway. Approximately 79 % of sitagliptin is excreted unchanged in the urine.
Following a [^{14}C]sitagliptin oral dose, approximately 16 % of the radioactivity was excreted as metabolites of sitagliptin. Six metabolites were detected at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin. In vitro studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin was CYP3A4, with contribution from CYP2C8.
In vitro data showed that sitagliptin is not an inhibitor of CYP isoenzymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6, and is not an inducer of CYP3A4 and CYP1A2.

Elimination

Following administration of an oral [^{14}C]sitagliptin dose to healthy subjects, approximately 100 % of the administered radioactivity was eliminated in faeces (13 %) or urine (87 %) within one week of dosing. The apparent terminal $t_{½}$ following a 100-mg oral dose of sitagliptin was approximately 12.4 hours. Sitagliptin accumulates only minimally with multiple doses. The renal clearance was approximately 350 mL/min.

Elimination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion. Sitagliptin is a substrate for human organic anion transporter-3 (hOAT-3), which may be involved in the renal elimination of sitagliptin. The clinical relevance of hOAT-3 in sitagliptin transport has not been established. Sitagliptin is also a substrate of p-glycoprotein, which may also be involved in mediating the renal elimination of sitagliptin. However, ciclosporin, a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin. Sitagliptin is not a substrate for OCT2 or OAT1 or PEPT1/2 transporters. In vitro, sitagliptin did not inhibit OAT3 (IC50=160 μM) or p-glycoprotein (up to 250 μM) mediated transport at therapeutically relevant plasma concentrations. In a clinical study sitagliptin had a small effect on plasma digoxin concentrations indicating that sitagliptin may be a mild inhibitor of p-glycoprotein.

Characteristics in patients

The pharmacokinetics of sitagliptin were generally similar in healthy subjects and in patients with type 2 diabetes.

Renal impairment

A single-dose, open-label study was conducted to evaluate the pharmacokinetics of a reduced dose of sitagliptin (50 mg) in patients with varying degrees of chronic renal impairment compared to normal healthy control subjects. The study included patients with renal impairment classified on the basis of creatinine clearance as mild (50 to < 80 mL/min), moderate (30 to < 50 mL/min), and severe (< 30 mL/min), as well as patients with end-stage renal disease (ESRD) on haemodialysis.

Patients with mild renal impairment did not have a clinically meaningful increase in the plasma concentration of sitagliptin as compared to normal healthy control subjects. An approximately 2-fold increase in the plasma AUC of sitagliptin was observed in patients with moderate renal impairment, and an approximately 4-fold increase was observed in patients with severe renal impairment and in patients with ESRD on haemodialysis, as compared to normal healthy control subjects. Sitagliptin was modestly removed by haemodialysis (13.5 % over a 3- to 4-hour haemodialysis session starting 4 hours post-dose).

Hepatic impairment

No dose adjustment for sitagliptin is necessary for patients with mild or moderate hepatic impairment (Child-Pugh score ≤ 9). There is no clinical experience in patients with severe hepatic impairment (Child-Pugh score > 9). However, because sitagliptin is primarily renally eliminated, severe hepatic impairment is not expected to affect the pharmacokinetics of sitagliptin.

Elderly

No dose adjustment is required based on age. Age did not have a clinically meaningful impact on the pharmacokinetics of sitagliptin based on a population pharmacokinetic analysis of Phase I and Phase II data. Elderly subjects (65 to 80 years) had approximately 19 % higher plasma concentrations of sitagliptin compared to younger subjects.

Paediatric
No studies with sitagliptin have been performed in paediatric patients.

Other patient characteristics
No dose adjustment is necessary based on gender, race, or body mass index (BMI). These characteristics had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data.

Metformin

Absorption
After an oral dose of metformin, tmax is reached in 2.5 h. Absolute bioavailability of a 500 mg metformin tablet is approximately 50-60 % in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30 %.
After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear. At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24-48 h and are generally less than 1 µg/mL. In controlled clinical trials, maximum metformin plasma levels (C_{max}) did not exceed 4 µg/mL, even at maximum doses.
Food decreases the extent and slightly delays the absorption of metformin. Following administration of a dose of 850 mg, a 40 % lower plasma peak concentration, a 25 % decrease in AUC and a 35 min prolongation of time to peak plasma concentration was observed. The clinical relevance of this decrease is unknown.

Distribution
Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean Vd ranged between 63 – 276 L.

Biotransformation
Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination
Renal clearance of metformin is > 400 mL/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 h. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

5.3 PRE-CLINICAL SAFETY DATA:

No animal studies have been conducted with Gvia-M.

In 16-week studies in which dogs were treated with either metformin alone or a combination of metformin and sitagliptin, no additional toxicity was observed from the combination. The NOEL in these studies was observed at exposures to sitagliptin of approximately 6 times the human exposure and to metformin of approximately 2.5 times the human exposure.
The following data are findings in studies performed with sitagliptin or metformin individually.

Sitagliptin
Renal and liver toxicity were observed in rodents at systemic exposure values 58 times the human exposure level, while the no-effect level was found at 19 times the human exposure level. Incisor teeth abnormalities were observed in rats at exposure levels 67 times the clinical exposure level; the no-effect level for this finding was 58-fold based on the 14-week rat study. The relevance of these findings for humans is unknown. Transient treatment-related physical signs, some of which suggest neural toxicity, such as open-mouth breathing, salivation, white foamy emesis, ataxia, trembling, decreased activity, and/or hunched posture were observed in dogs at exposure levels approximately 23 times the clinical exposure level. In addition, very slight to slight skeletal muscle degeneration was also observed histologically at doses resulting in systemic exposure levels of approximately 23 times the human exposure level. A no-effect level for these findings was found at an exposure 6-fold the clinical exposure level.
Sitagliptin has not been demonstrated to be genotoxic in preclinical studies. Sitagliptin was not carcinogenic in mice. In rats, there was an increased incidence of hepatic adenomas and carcinomas at systemic exposure levels 58 times the human exposure level. Since hepatotoxicity has been shown to correlate with induction of hepatic neoplasia in rats, this increased incidence of hepatic tumours in rats was likely secondary to chronic hepatic toxicity at this high dose. Because of the high safety margin (19-fold at this no-effect level), these neoplastic changes are not considered relevant for the situation in humans.
No treatment related effects on fertility were observed in male and female rats given sitagliptin prior to and throughout mating.
In a pre-/post-natal development study performed in rats sitagliptin showed no adverse effects.
Reproductive toxicity studies showed a slight treatment-related increased incidence of foetal rib malformations (absent, hypoplastic and wavy ribs) in the offspring of rats at systemic exposure levels more than 29 times the human exposure levels. Maternal toxicity was seen in rabbits at more than 29 times the human exposure levels. Because of the high safety margins, these findings do not suggest a relevant risk for human reproduction. Sitagliptin is secreted in considerable amounts into the milk of lactating rats (milk/plasma ratio: 4:1).

Metformin
Preclinical data for metformin reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6.0 PHARMACEUTICAL PARTICULARS
7.1 List of Excipients

Tablet core: PVP K-30, HPMC (Pharma Coat), Sodium Lauryl Sulfate and Magnesium stearate

Film coating: HPMC (Pharma Coat), Talcum, Titanium Dioxide, P.E.G 6000 (Flakes), Povidone (PVP K-30), Dye Yellow Sicopharm.

7.2 Incompatibilities
None known

7.3 Shelf life
24 months

7.4 storage condition
Store below 30^{0}C.

7.5 Nature and contents of container
Alu/Alu blister of 60's with leaf insert and bleach board carton.

8. MARKETING AUTHORISATION HOLDER
Genix Pharma (Pvt) Ltd**,** 44, 45-B, Korangi Creek Road, Karachi 75190-Pakistan

9. MARKETING AUTHORISATION NUMBER(S)
Genix Pharma (Pvt.) Ltd

10. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Not applicable

11. DATE OF REVISION OF THE TEXT
Not applicable