Gvia®-M

جیویا-ایم

(Sitagliptin/Metformin HCl)

(سیٹاگلپٹن/میٹ فورمن ہائیڈروکلورائیڈ)

50mg/500mg 50mg/850mg 50mg/1000mg

Tablets B.P.

۵۰ملی گرام/۵۰۰ملی گرام ۵۰ملی گرام/۸۵۰ملی گرام

۵۰ملی گرام/۱۰۰۰ملی گرام ٹیبلٹس بی۔پی۔

QUALITATIVE AND QUANTITATIVE COMPOSITION

Gvia®-M Tablets 50mg/500mg: Each film-coated tablet contains:
Sitagliptin Phosphate U.S.P. eq.to
Sitagliptin.....50mg, Metformin HCl U.S.P. .....500mg, B.P.
Gvia®-M Tablets 50mg/850mg:
Each film-coated tablet contains: Sitagliptin Phosphate U.S.P. eq. to
Sitagliptin.....50mg, Metformin HCl U.S.P. 850mg
Gvia®-M Tablets 50mg/1000mg: Each film-coated tablet contains:
Sitagliptin Phosphate U.S.P. eq.to
Sitagliptin.....50mg, Metformin HCl U.S.P. 1000mg

WARNING: Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, & resistant bradya rrhythmias. Symptoms included malaise, myalgia, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio, and metformin plasma levels generally >5 mcg/mL. • Risk factors include renal impairment, concomitant use of certain drugs, age ≥65 years old, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment. Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high-risk groups are provided in the Full Prescribing Information • If lactic acidosis is suspected, discontinue Gvia®-M and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.

DESCRIPTION:

Gvia-M (Sitagliptin/Metformin HCl) tablets contain two oral antihyperglycemic drugs used in the management of type 2 diabetes: Sitagliptin and Metformin Hydrochloride.

CLINICAL PHARMACOLOGY:

Mechanism of Action: Gvia-M combines two antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes mellitus: sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, and metformin hydrochloride, a member of the biguanide class. **Sitagliptin:** Sitagliptin is a DPP-4 inhibitor, which is believed to exert its action in patients with type 2 diabetes by slowing the inactivation of incretin hormones. Concentrations of the active intact hormones are increased by sitagliptin, thereby increasing and prolonging the action of these hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. These hormones are rapidly inactivated by the enzyme DPP-4. Metformin hydrochloride Metformin is an antihyperglycemic agent which improves glucose tolerance 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. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects (except in special circumstances).

Pharmacokinetics:

Absorption: Sitagliptin: The absolute bioavailability of sitagliptin is approximately 87%. Co-administration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics of sitagliptin.
Metformin hydrochloride: The absolute bioavailability of a metformin hydrochloride 500mg tablet given under fasting condition is approximately 50-60%.
Distribution: Sitagliptin: The mean volume of distribution at steady state following a single 100mg intravenous dose of sitagliptin is approximately 198 liters. The fraction of sitagliptin re-

versibly bound to plasma proteins is low (38%).
Metformin hydrochloride: The apparent volume of distribution (V/F) of metformin following single oral doses of metformin hydrochloride tablets 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound.
Metabolism: Sitagliptin: The primary enzyme responsible for the limited metabolism of sitagliptin is CYP3A4, with contribution from CYP2C8. **Metformin hydrochloride:** 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. **Elimination: Sitagliptin:** Approximately 79% of sitagliptin is excreted unchanged in the urine with metabolism being a minor pathway of elimination.
Metformin hydrochloride: 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.

INDICATIONS: **For adult patients with type 2 diabetes mellitus, Gvia-M is indicated:** -as an adjunct to diet and exercise to improve glycemic control when treatment with both sitagliptin and metformin is appropriate. - in combination with a sulphonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea. - as triple combination therapy with a peroxisome proliferator-activated receptor gamma (PPAR) agonist (i.e., a thiazolidinedione) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a PPAR agonist. - as add-on to insulin (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycemic control in patients when stable dose of insulin and metformin alone do not provide adequate glycemic control. **Important Limitations of Use:** Gvia-M should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

CONTRAINDICATIONS:
Gvia-M (Sitagliptin/Metformin HCl) is contraindicated in patients with: -Renal disease or renal dysfunction, e.g., as suggested by serum creatinine levels ≥ 1.5 mg/dL [males], ≥ 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. acute conditions with the potential to alter renal function such as: - dehydration, - severe infection, - intravascular administration of iodinated contrast agents - acute or chronic disease which may cause tissue hypoxia such as: - cardiac or respiratory failure, - recent myocardial infarction, - shock. - hepatic impairment; - acute alcohol intoxication, alcoholism; - breast-feeding. -Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. -History of a serious hypersensitivity reaction to Gvia-M or sitagliptin (one of the components of Gvia-M), such as anaphylaxis or angioedema.

INTERACTIONS:
Carbonic Anhydrase Inhibitors: Concomitant use of Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) with Gvia-M may increase the risk of lactic acidosis. Consider more frequent monitoring of these patients. **Drugs that Reduce Metformin Clearance:** Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter- 2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) may increase the risk for lactic acidosis. Consider the benefits and risks of concomitant use. **Alcohol:** Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving Gvia-M.
Insulin Secretagogues or Insulin: Coadministration 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.
Use of Metformin with Other Drugs: Certain drugs such as thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetic, calcium channel blocking drugs, and isoniazid tend to produce hyperglycemia and may lead to loss of glycemic control.
Digoxin: Patients receiving digoxin should be monitored appropriately. No dosage adjustment of digoxin or Gvia-M is recommended.
Iodinated contrast agents: Gvia-M must be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been

re-evaluated and found to be stable.
ACE-inhibitors: may decrease the blood glucose levels. If necessary, the dose of the anti-hyperglycemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.
Combinations requiring precautions for use: Some medicinal products can adversely affect renal function, which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting, or using such products in combination with metformin, close monitoring of renal function is necessary.

USE IN SPECIFIC POPULATION:

Pregnancy: Gvia-M should not be used during pregnancy. **Breastfeeding:** Gvia-M must not be used in women who are breast-feeding. **Pediatric Use:** Safety and effectiveness of Gvia-M in pediatric patients under 18 years have not been established. **Elderly patient:** Because sitagliptin and metformin are substantially excreted by the kidney, and because aging can be associated with reduced renal function, renal function should be assessed more frequently in elderly patients. **Renal patient:** Gvia-M is not recommended in patients with an eGFR between 30 and less than 45 mL/min/1.73 m2 because these patients require a lower dosage of sitagliptin than what is available in the fixed dose combination Gvia-M product.
Hepatic impairment: Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. Gvia-M is not recommended in patients with hepatic impairment.

WARNINGS AND PRECAUTIONS:

Lactic acidosis: Metformin-associated lactic acidosis.
Pancreatitis: 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.
Vitamin B12 Levels: 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.

ADVERSE REACTIONS:

Common: Hypoglycemia, nausea, flatulence, vomiting.
Uncommon: Somnolence, diarrhea, constipation, upper abdominal pain, pruritus, hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions in-cluding Stevens-Johnson syndrome; upper respiratory tract infection; hepatic enzyme elevations; acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis; worsening renal function, including acute renal failure (sometimes requiring dialysis); severe and disabling arthralgia; bullous pemphigoid; headache; myalgia; pain in extremity; back pain; mouth ulceration; stomatitis; cholestatic, hepatocellular, and mixed hepatocellular liver injury.

DOSAGE AND ADMINISTRATION:

Recommended Dosing: The dosage of Gvia-M should be individualized on the basis of the patient's current regimen, effectiveness & tolerability while not exceeding the maximum daily dose of 100 mg sitagliptin and 2000 mg metformin. Gvia-M should generally be given twice daily with meals, with gradual dose escalation to reduce the gastrointestinal (GI) side effects due to metformin.
The following doses are available: 50 mg sitagliptin/500 mg metformin hydrochloride, 50 mg sitagliptin/850 mg metformin hydrochloride 50 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. 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. **Special populations:** Renal impairment: No dose adjustment is needed for patients with mild renal impairment (glomerular filtration rate [GFR] 60 mL/min). The maximum daily dose of metformin should preferably be divided into

2-3 daily doses. Factors that may increase the risk of lactic acidosis should be reviewed before considering initiation of metformin in patients with GFR < 60 mL/min.

GFR mL/min	Metformin	Sitagliptin
60-89	Maximum daily dose is 3000 mg. Dose reduction may be considered in relation to declining renal function.	Maximum daily dose is 100 mg.
45-59	Maximum daily dose is 2000 mg. The starting dose is at most half of the maximum dose.	Maximum daily dose is 100 mg.
30-44	Maximum daily dose is 1000 mg. The starting dose is at most half of the maximum dose.	Maximum daily dose is 50 mg.
< 30	Metformin is contraindicated.	Maximum daily dose is 25 mg.

Overdosage:

Sitagliptin: In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy as indicated by the patient's clinical status. Prolonged hemodialysis may be considered if clinically appropriate.
Metformin Hydrochloride: Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Lactic acidosis has been reported in approximately 32% of metformin overdose cases. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

DOSAGE

As directed by the physician.

INSTRUCTIONS

Store below 30°C. Protect from heat, light & moisture.
Keep all medicines out of the reach of children.

PRESENTATION

Gvia®-M (Sitagliptin/Metformin HCl) Tablets 50mg/500mg are available in Alu-Alu blister pack of 4 x 7's.
Gvia®-M (Sitagliptin/Metformin HCl) Tablets 50mg/850mg are available in Alu-Alu blister pack of 4 x 7's.
Gvia®-M (Sitagliptin/Metformin HCl) Tablets 50mg/1000mg are available in Alu-Alu blister pack of 4 x 7's.

علامات/طریقہ استعمال:

جیویا۔ایم ٹائپ II ذیابیطس میں مبتلا مریضوں کے علاج کے لئے تجویز کردہ ہے۔

مضر اثرات:

متلی، بدہضمی، اُلٹی، غنودگی، قبض، پرورائٹس، الرجی وغیرہ۔

احتیاطی تدابیر:

جیویا۔ایم یا سیٹاگلپٹن سے حساس مریضوں میں جیویا۔ایم کا استعمال ممنوع ہے۔
حاملہ خواتین، دودھ پلانے والی ماؤں اور جگر کے مریضوں میں جیویا۔ایم کا استعمال ممنوع ہے۔
میٹفورمن سے منسلک لیکٹک ایسیڈوسس۔
لبلبہ کی سوزش کا خدشہ ہوتے ہی جیویا۔ایم کا استعمال فوری طور پر روک دیں۔
جیویا۔ایم کے استعمال کے دوران عمر رسیدہ افراد میں گردوں کی کارکردگی مستقل طور پر مانیٹر کریں۔
جن مریضوں کا ای جی ایف آر ۳۰ سے ۴۵ کے درمیان ہو، ان میں جیویا۔ایم کا استعمال ممنوع ہے۔
خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
ہدایات: ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔سورج کی روشنی، گرمی اور نمی سے محفوظ رکھیں۔
تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔

For detailed information:

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ISO 14001:2015 CERTIFIED TÜV AUSTRIA — ISO 14001:2015
ISO 45001:2018 CERTIFIED TÜV AUSTRIA — ISO 45001:2018

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