Gvia®-MXR

(Sitagliptin/Metformin HCl)
Prolonged-release Tablets B.P.

50mg / 500mg | 50mg / 1000mg | 100mg / 1000mg

جیویا-ایم ایکس آر

(سیٹاگلپٹن/میٹ فورمن ہائیڈروکلورائیڈ) ٹیبلٹس بی۔پی۔

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QUALITATIVE AND QUANTITATIVE COMPOSITION

Gvia®-M XR Prolonged-release tablets B.P. 50mg/500mg:

Each film-coated Prolonged-release tablet contains:

Sitagliptin phosphate U.S.P eq to Sitagliptin.....50mg (as Immediate Release coating)

Metformin HCl U.S.P. .....500mg (as Extended Release Core)

Gvia®-M XR Prolonged-release tablets B.P. 50mg/1000mg:

Each film-coated Prolonged-release tablet contains:

Sitagliptin phosphate U.S.P eq to Sitagliptin.....50mg (as Immediate Release coating)

Metformin HCl U.S.P. .....1000mg (as Extended Release Core)

Gvia®-M XR Prolonged-release tablets B.P. 100mg/1000mg:

Each film-coated Prolonged-release tablet contains:

Sitagliptin phosphate U.S.P. eq to Sitagliptin (as immediate release layer) 100mg

Metformin HCl U.S.P (as extended release core) 1000mg,

WARNING: LACTIC ACIDOSIS

-Post marketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio, and metformin plasma levels generally >5 mcg/mL. Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment. If metformin-associated lactic acidosis is suspected, immediately discontinue Gvia®-MXR and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.

DESCRIPTION:

Gvia®-MXR tablets contain two oral antidiabetic medications used in the management of type 2 diabetes: sitagliptin and metformin hydrochloride extended-release.

CLINICAL PHARMACOLOGY:

Mechanism of Action: Gvia®-MXR tablets combine two antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in adults with type 2 diabetes mellitus: sitagliptin, a dipeptidyl peptidase 4 (DPP-4) inhibitor, and metformin hydrochloride extended-release, a member of the biguanide class.

Sitagliptin: Sitagliptin is a DPP-4 inhibitor, which exerts its actions in patients with type 2 diabetes by slowing the inactivation of incretin hormones.

Metformin hydrochloride: Metformin is a biguanide that improves glycemic control in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose.

Pharmacodynamics: Sitagliptin: in patients with type 2 diabetes mellitus, administration of sitagliptin led to inhibition of DPP-4 enzyme activity for a 24-hour period. **Sitagliptin and Metformin hydrochloride Coadministration:** Coadministration of sitagliptin and metformin had an additive effect on active GLP-1 concentrations. Sitagliptin, but not metformin, increased active GIP concentrations. **Pharmacokinetics:** After administration of two Gvia®-MXR 50 mg/1000 mg tablets once daily with the evening meal for 7 days in healthy adult subjects, steady-state for sitagliptin and metformin is reached by Day 4 and 5, respectively.

Absorption: Gvia®-MXR After administration of Gvia®-MXR tablets once daily, the median Tmax value for sitagliptin and metformin at steady state is approximately 3 and 8 hours post dose, respectively.

Effect of Food: After administration of Gvia®-MXR with a high-fat breakfast, the AUC for metformin increased 62%, the Cmax for metformin decreased by 9%, and the median Tmax for metformin occurred 2hours later relative to the fasted state.

Distribution: Sitagliptin: The mean volume of distribution at steady state following a single 100-mg intravenous dose of sitagliptin to healthy subjects is approximately 198 liters. The fraction of sitagliptin reversibly bound to plasma proteins is low (38%). Metformin hydrochloride: Distribution studies with extended-release metformin have not been conducted; however, the apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin hydrochloride tablets 850 mg averaged 654 ± 358 L.

Elimination: Sitagliptin: Approximately 79% of sitagliptin is excreted unchanged in the urine with metabolism being a minor pathway of elimination. The apparent terminal t1/2 following a 100mg oral dose of sitagliptin was approximately 12.4 hours and renal clearance was approximately 350 mL/min.

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. **Metabolism: Sitagliptin:** The primary enzyme responsible for the limited metabolism of sitagliptin was CYP3A4, with contribution from CYP2C8. Metformin hydrochloride: Metabolism studies with extended-release metformin tablets have not been conducted. **Excretion: Sitagliptin:** Elimination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion. **Metformin hydrochloride:** Elimination of metformin occurs primarily via renal excretion. Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination.

INDICATIONS AND USAGE: Gvia®-MXR 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 extended-release is appropriate. Important Limitations of Use Gvia-M®XR should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Gvia®-MXR 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®-MXR.

CONTRAINDICATIONS : Gvia®-MXR 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®-MXR or sitagliptin, such as anaphylaxis or angioedema

INTERACTIONS: -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®-MXR, 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. Careful patient monitoring and dose adjustment of Gvia®-MXR. **-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, phenothiazine, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetic, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving Gvia®-MXR. the patient should be closely observed to maintain adequate glycemic control.

USE IN SPECIFIC POPULATION: Pregnancy: Category B: The safety of Gvia-M®XR in pregnant women is not known. Gvia®-MXR should be used during pregnancy only if clearly needed. **Nursing Mothers:** It is not known whether sitagliptin or metformin are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Gvia®-MXR is administered to a nursing woman. **Pediatric Use:** Safety and effectiveness of Gvia®-MXR in pediatric patients under 18 years have not been established.**Geriatric Use:** Gvia®-MXR Because sitagliptin and metformin are substantially excreted by the kidney, and because aging can be associated with reduced renal function, Gvia®-MXR should be used with caution as age increases.

PRECAUTIONS: -Lactic Acidosis: Lactic acidosis is a serious, metabolic complication that can occur due to metformin accumulation during treatment with Gvia®-MXR and is fatal in approximately 50% of cases. 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:** After initiation of Gvia®-MXR, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, Gvia®-MXR should promptly be discontinued and appropriate management should be initiated. **-Impaired Hepatic Function:** Since impaired hepatic function has been associated with some cases of lactic acidosis, Gvia®-MXR should generally be avoided in patients with clinical or

laboratory evidence of hepatic disease. **-Assessment of Renal Function:** Metformin and sitagliptin are 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®-MXR is contraindicated in patients with renal impairment. Sitagliptin: Sitagliptin There have been post marketing reports of worsening renal function in patients taking sitagliptin with or without metformin, including acute renal failure, sometimes requiring dialysis. Before initiation of therapy with Gvia®-MXR and at least annually thereafter, renal function should be assessed and verified as normal. **-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. **-Alcohol Intake:** Alcohol potentiates the effect of metformin on lactate metabolism. Patients should be warned against excessive alcohol intake while receiving Gvia®-MXR. **-Surgical Procedures:** Use of Gvia®-MXR 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®-MXR 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®-MXR must be stopped immediately and other appropriate corrective measures initiated. **-Use with Medications Known to Cause Hypoglycemia: Sitagliptin:** 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. **-Concomitant Medications Affecting Renal Function or Metformin Disposition:** Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion, should be used with caution. **-Radiologic Studies with Intravascular Iodinated:** Contrast Materials Intravascular contrast studies with iodinated materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast materials) can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. **-Hypoxic States:** Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on Gvia®-MXR therapy, the drug should be promptly discontinued. -Loss of Control of Blood Glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold Gvia-M®XR and temporarily administer insulin. Gvia®-MXR may be reinstituted after the acute episode is resolved. **-Hypersensitivity Reactions:** If a hypersensitivity reaction is suspected, discontinue Gvia®-MXR, assess for other potential causes for the event, and institute alternative treatment for diabetes.

ADVERSE REACTIONS: Diarrhea, upper respiratory tract infection, headache, nausea, vomiting, abdominal pain, constipation, arthralgia, hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions including 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; myalgia; pain in extremity; back pain.

DOSAGE AND ADMINISTRATION: - Recommended Dosage The dose of Gvia®-MXR 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 • In patients not currently treated with metformin, the recommended total daily starting dose of Gvia®-MXR is 100 mg sitagliptin and 1000 mg metformin hydrochloride (HCl) extended release. Patients with inadequate glycemic control on this dose of metformin can be titrated gradually, to reduce gastrointestinal side effects associated with metformin, up to the maximum recommended daily dose. • In patients already treated with metformin, the recommended total daily starting dose of Gvia®-MXR is 100 mg sitagliptin and the previously prescribed dose of metformin. • For patients taking metformin immediate-release 850 mg twice daily or 1000 mg twice daily, the recommended starting dose of Gvia®-MXR is two 50 mg sitagliptin/1000 mg metformin hydrochloride extended-release tablets taken together once daily. • Patients with inadequate glycemic control on this dose of metformin can be titrated gradually, to reduce gastrointestinal side effects associated with metformin, up to the maximum recommended daily dose. -Gvia®-MXR should

be administered with food to reduce the gastrointestinal side effects associated with the metformin component. Gvia®-MXR should be given once daily with a meal preferably in the evening. Gvia®-MXR should be swallowed whole. The tablets must not be split, crushed, or chewed before swallowing. The 100 mg sitagliptin/1000 mg metformin hydrochloride extended-release tablet should be taken as a single tablet once daily. Patients using two Gvia®-MXR tablets (such as two 50 mg sitagliptin/500 mg metformin hydrochloride extended-release tablets or two 50 mg sitagliptin/1000 mg metformin hydrochloride extended-release tablets) should take the two tablets together once daily. Patients treated with an insulin secretagogue or insulin Co-administration of Gvia®-MXRwith an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower doses of the insulin secretagogue or insulin to reduce the risk of hypoglycemia. **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 clinicall appropriate. It is not known if sitagliptin is dialyzable by peritoneal dialysis. **Metformin hydrochloride:** Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. 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 at 25°C, excursions permitted to 15°C - 30°C.

Protect from sunlight and moisture. Keep all medicines out of the reach of children.

PRESENTATION

Gvia®-M (Sitagliptin/ Metformin HCl) XR Tablets 100mg/1000mg are available in Alu-Alu blister pack of 14 tablets.

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علامات/طریقہ استعمال: جیویا-ایم ایکس آر ٹیبلٹس ٹائپ ۲ ذیابطیس میلائٹس میں مبتلا مریضوں کے علاج کے لئے تجویز کردہ ہے۔

مضر اثرات: دست، سر درد، متلی، اُلٹی، الرجی، کمر درد، قبض۔

احتیاطی تدابیر: حاملہ خواتین اور دودھ پلانے والی مائیں ضرورت پڑنے کے پیش نظر صرف ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

بچے اور بزرگ احتیاط سے استعمال کریں۔ لیکٹک ایسیڈوسس کا خدشہ ہوتے ہی جیویا-ایم ایکس آر کا استعمال فوری طور پر روک دیں۔

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات: ۲۵ ڈگری سینٹی گریڈ پر رکھیں، محفوظ رکھنے کی حد ۱۵ سے ۳۰ ڈگری سینٹی گریڈ ہے۔

سورج کی روشنی اور نمی سے محفوظ رکھیں۔ تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔

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