GALZA-MET™

(VILDAGLIPTIN + METFORMIN HCl)

TABLET

گیلزا-میٹ

COMPOSITION:
Galza-Met 50/500 Tablet :
Each film coated tablet contains:
Vildagliptin ..... 50 mg.
Metformin HCl ..... 500 mg.

Product Specs.: Innovator

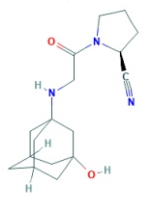
Galza-Met 50/850 Tablet :
Each film coated tablet contains:
Vildagliptin ..... 50 mg.
Metformin HCl ..... 850 mg.

Product Specs.: Innovator

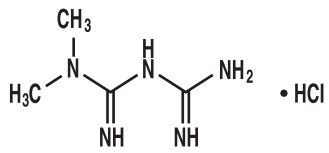
Galza-Met 50/1000 Tablet:
Each film coated tablet contains:
Vildagliptin ..... 50 mg.
Metformin HCl ..... 1000 mg.

Product Specs.: Innovator

DESCRIPTION :
GALZA-Met combines two antihyperglycemic agents vildagliptin, a member of the DPP-4 (dipeptidyl-peptidase-4) inhibitor class and metformin hydrochloride, a member of the biguanide class.
Vildagliptin: Chemically vildagliptin is (S)-1-[2-(3-Hydroxy-adamantan-1-ylamino)acetyl]pyrrolidine-2-carbonitrile with molecular formula $C_{17}H_{25}N_3O_2$ and molecular weight of 303.406 and its structural formula is:



Metformin hydrochloride: Chemically Metformin hydrochloride is Imidodicarbinimidic, N, N-dimethyl-, monohydrochloride, a compound with a molecular formula of $C_4H_{11}N_5$•HCl and a molecular weight of 165.63. The structural formula is:



CLINICAL PHARMACOLOGY:
Mechanism of Action: GALZA-Met combines two antihyperglycemic agents with different mechanisms of action to improve glycaemic control in patients with type 2 diabetes: vildagliptin, a member of the DPP-4 (dipeptidyl-peptidase-4) inhibitor class and metformin hydrochloride, a member of the biguanide class. Clinical studies established an added benefit of vildagliptin in patients with inadequately controlled type 2 diabetes while on metformin hydrochloride therapy.
Vildagliptin: Vildagliptin, a member of the islet enhancer class, is a potent and selective dipeptidylpeptidase-4 (DPP-4) inhibitor that improves glycaemic control. The administration of vildagliptin results in rapid and complete inhibition of DPP-4 activity. In patients with type 2 diabetes, administration of vildagliptin led to inhibition of DPP-4 enzyme activity for a 24-hour period. Vildagliptin inhibition of DPP-4 results in increased fasting and postprandial endogenous levels of the incretin hormones GLP-1 (glucagon-like peptide 1) and GIP (glucose-dependent insulinotropic polypeptide. By increasing the endogenous levels of these incretin hormones, vildagliptin enhances the sensitivity of beta cells to glucose, resulting in improved glucose-dependent insulin secretion.
Metformin: Metformin is a biguanide that improves glycemic control in patients with type 2 diabetes mellitus, 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 either patient with type 2 diabetes mellitus or healthy subjects except in certain circumstances and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.
Pharmacokinetics:
Absorption:
GALZA-Met: In the bioequivalence studies of the combination Vildagliptin and metformin, versus free combination of vildagliptin and metformin hydrochloride, the area under the curve (AUC) and maximum concentration (C_{max}) of both the vildagliptin component and the metformin hydrochloride component of the combination were demonstrated to be bioequivalent to that of free combination tablets.
Vildagliptin: Following oral administration in the fasting state, vildagliptin is rapidly absorbed with peak plasma concentrations observed at 1.75 hours. Co-administration with food slightly decreases the rate of absorption of vildagliptin, as characterized by a 19% decrease in peak concentrations, and a delay in the time to peak plasma concentration to 2.5 hours. There is no change in the extent of absorption, and food does not alter the overall exposure (AUC).
Metformin Hydrochloride: The absolute bioavailability of a 500 mg metformin hydrochloride tablet given under fasting conditions is approximate 50 to 60%. Food decreases the extent of and slightly delays the absorption of metformin hydrochloride, as shown by approximately a 40% lower mean peak plasma concentration (C_{max}), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35-minute prolongation of time to peak plasma concentration (T_{max})
Distribution:
Vildagliptin: The plasma protein binding of vildagliptin is low (9.3%), and vildagliptin distributes equally between plasma and red blood cells. The mean volume of distribution of vildagliptin at steady state after intravenous administration (Vss) is 71 L, suggesting extravascular distribution.
Metformin Hydrochloride: The apparent volume of distribution (V/F) of metformin hydrochloride averaged 654 ± 358 L. Metformin hydrochloride is negligibly bound to plasma proteins. Metformin hydrochloride partitions into erythrocytes, most likely as a function of time. Steady state plasma concentrations of metformin hydrochloride are reached within 24 to 48 hours and are generally <1 microgram/mL.
Metabolism:
Vildagliptin: Metabolism is the major elimination pathway for vildagliptin in humans, accounting for 69% of the dose. The major metabolite, LAY151, is pharmacologically inactive, accounting for 57% of the dose, followed by the amide hydrolysis product (4% of the dose). DPP-4 contributes partially to the hydrolysis of vildagliptin as shown in an in-vivo study using DPP-4 deficient rats. Vildagliptin is not metabolized by cytochrome P450 enzymes to any quantifiable extent.
Excretion and Elimination:
Vildagliptin: Following oral administration of [14C]-vildagliptin, approximately 85% of the dose is excreted into the urine and 15% of the dose is recovered in the faeces. Renal excretion of the unchanged vildagliptin accounts for 23% of the dose after oral administration. The elimination half-life after oral administration is approximately 3 hours and is independent of dose.
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.
Obesity:
Vildagliptin: BMI does not show any impact on the pharmacokinetic parameters of vildagliptin. DPP-4 inhibition by vildagliptin was unaffected by BMI.
Hepatic Impairment:
Vildagliptin: The use of vildagliptin is not recommended in patients with hepatic impairment including patients with a pre-treatment ALT or AST >2.5X the upper limit of normal.
Metformin Hydrochloride: No pharmacokinetic studies of metformin hydrochloride have been conducted in subjects with hepatic insufficiency.
Renal Impairment:
Vildagliptin: Based on the evaluation of safety, tolerability, and effectiveness of vildagliptin in patients whose GFR values were <60 mL/min, no dosage adjustment is required in patients with mild renal impairment. The use of vildagliptin is not recommended in patients with moderate or severe renal impairment or in patients with ESRD on haemodialysis.
Metformin Hydrochloride: In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin hydrochloride is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance.
Elderly:
Vildagliptin: DPP-4 inhibition by vildagliptin is not affected by age in the age groups studied.
Metformin Hydrochloride: Change in metformin hydrochloride pharmacokinetics with aging is primarily accounted for by a change in renal function. GALZA-Met treatment should not be initiated in patients ⩾80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced.
Pediatric: No pharmacokinetic data available.

INDICATIONS AND USAGE:
GALZA-Met is indicated: As an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus whose diabetes is not adequately controlled on metformin hydrochloride or vildagliptin alone or who are already treated with the combination of vildagliptin and metformin hydrochloride, as separate tablets.

DOSAGE AND ADMINISTRATION:
In using GALZA-Met do not exceed the maximum daily dose of vildagliptin (100 mg). The recommended starting dose of GALZA-Met should be based on the patient's current regimen of vildagliptin and/or metformin hydrochloride.
Administration: GALZA-Met should be given with meals to reduce the gastrointestinal side effects associated with metformin hydrochloride.
- Starting dose for patients inadequately controlled on vildagliptin monotherapy Based on the usual starting doses of metformin hydrochloride (850 mg once daily), GALZA-Met may be initiated at the 50 mg/1000 mg tablet strength once daily and gradually titrated after assessing adequacy of therapeutic response.
- Starting dose for patients inadequately controlled on metformin hydrochloride Monotherapy Based on the patient's current dose of metformin hydrochloride, GALZA-Met may be initiated at either the 50 mg/850 mg or 50 mg/1,000 mg tablet strength twice daily.
- Starting dose for patients switching from combination therapy of vildagliptin plus metformin hydrochloride as separate tablets, GALZA-Met may be initiated with either the 50 mg/850 mg or 50 mg/1,000 mg tablet strength based on the dose of vildagliptin or metformin already being taken.

Dose Modification Recommendations:
- ***Patients with renal impairment:*** GALZA-Met should not be used in patients with renal failure or renal dysfunction, e.g. serum creatinine levels ⩾1.5 mg/dL (>135 micromol/L) in males and ⩾1.4 mg/dL (>110 micromol/L) in female.
- ***Patients with hepatic impairment:*** GALZA-Met is not recommended in patients with clinical or laboratory evidence of hepatic impairment including patients with a pre-treatment ALT or AST >2.5X the upper limit of normal (see Special warnings and precautions for use).
- ***Elderly:*** Elderly patients taking GALZA-Met should have their renal function monitored regularly. GALZA-Met should only be used in elderly patients with normal renal function
- ***Paediatric patients:*** Safety and effectiveness of GALZA-Met in paediatric patients have not been established. Therefore, GALZA-Met is not recommended for use in children below 18 years of age.

CONTRAINDICATIONS:
Hypersensitivity:
GALZA-Met is contraindicated in patients with known hypersensitivity to vildagliptin or metformin hydrochloride Renal disease:
GALZA-Met is contraindicated in patients with renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ⩾1.5 mg/dL (>135 micromol/L) in males and ⩾1.4 mg/dL (>110 micromol/L) in females or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicaemia.
Congestive heart failure: GALZA-Met is contraindicated in patients with congestive heart failure requiring pharmacologic treatment.
Diabetic ketoacidosis: GALZA-Met is contraindicated in patients with acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.
Radiologic Studies: GALZA-Met should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function.

WARNINGS AND PRECAUTIONS:
Allergic Reactions: GALZA-Met is not a substitute for insulin in insulin-requiring patients. GALZA-Met should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.
Vildagliptin:
Hepatic impairment:
Vildagliptin is not recommended in patients with hepatic impairment, including patients with a pre-treatment ALT or AST >2.5X the upper limit of normal.
Liver enzyme monitoring:
LFTs should be performed prior to the initiation of treatment with GALZA-Met. LFTs should be monitored during GALZA-Met treatment at three-month intervals during the first year and periodically thereafter. Should an increase in AST or ALT of 3 X upper limit of normal or greater persist, withdrawal of therapy with GALZA-Met is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue GALZA-Met. Following withdrawal of treatment with GALZA-Met and LFT normalisation, GALZA-Met should not be reinitiated.
Metformin Hydrochloride:
Lactic Acidosis:
Lactic acidosis is a very rare but serious metabolic complication that can occur due to metformin accumulation. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/L and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, treatment with the medicinal product should be discontinued and the patient hospitalised immediately.
Monitoring of renal function:
Metformin hydrochloride is substantially excreted by the kidney, and the risk of metformin hydrochloride accumulation and lactic acidosis increases with the degree of renal function impairment. Patients with anticipated renal dysfunction, should have their renal function assessed more frequently. GALZA-Met should be discontinued if evidence of renal impairment is present.
Hypoxic states:
Cardiovascular collapse (shock), acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxaemia have been associated with lactic acidosis and may also cause prerenal azotmeia. If such events occur in patients receiving GALZA-Met therapy, the medication should be promptly discontinued.
Surgical procedures:
Use of GALZA-Met should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.
Alcohol intake:
Alcohol is known to potentiate the effect of metformin hydrochloride on lactate metabolism.
Patients should be warned against excessive alcohol intake while receiving GALZA-Met.
Impaired hepatic function:
Vitamin B12 levels: The metformin component of GALZA-Met has been associated with a decrease in serum vitamin B12 levels without clinical manifestations, in approximately 7% of patients.
Change in clinical status of patients with previously controlled type 2 diabetes:
A patient with type 2 diabetes previously well-controlled on GALZA-Met who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should promptly be evaluated for ketoacidosis and/or lactic acidosis. If acidosis of either form occurs, GALZA-Met must be stopped immediately and appropriate measures initiated.
Hypoglycaemia: Hypoglycaemia does not usually occur in patients receiving GALZA-Met alone, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or ethanol use. Elderly, debilitated or malnourished patients and those with adrenal or pituitary insufficiency or alcohol intoxication are susceptible to hypoglycaemic effects. Hypoglycaemia may be difficult to recognize in the elderly and in people taking betaadrenergic blocking drugs.
Loss of control of blood glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, surgery, etc., a temporary loss of glycaemic control may occur. At such times, it may be necessary to withhold GALZA-Met and temporarily administer insulin. GALZA-Met may be reinstituted after the acute episode is resolved.

DRUG INTERACTIONS:
No clinically relevant pharmacokinetic interaction was observed when vildagliptin (100 mg once daily) was co-administered with metformin hydrochloride (1,000 mg once daily). The following statements reflect the information available on the individual active substances
(vildagliptin and metformin).
Vildagliptin:
Vildagliptin has a low potential for drug interactions. Since vildagliptin is not a cytochrome P (CYP) 450 enzyme substrate nor does it inhibit nor induces CYP 450 enzymes, it is not likely to interact with co-medications that are substrates, inhibitors or inducers of these enzyme. vildagliptin does not affect metabolic clearance of co-medications metabolized by CYP 1A2, CYP 2C8, CYP 2C9, CYP 2C19, CYP 2D6, CYP2E1, and CYP 3A4/5. no clinically relevant interactions with other oral antidiabetics (glibenclamide, pioglitazone, metformin hydrochloride), amlodipine, digoxin, ramipril, simvastatin, valsartan or warfarin were observed after co-administration with vildagliptin.
Metformin Hydrochloride:
The following is known for metformin component:
Furosemide: Furosemide increased Cmax and blood AUC of metformin with no change in renal clearance of metformin. Metformin decreased Cmax, blood AUC of furosemide, with no change in renal clearance of furosemide.
Nifedipine: Nifedipine increased absorption, Cmax and AUC of metformin, and increased excretion of metformin in urine. Metformin had minimal effects on nifedipine.
Glyburide: Glyburide produced no changes in metformin PK/PD parameters. Decreases in Cmax, blood AUC of glyburide were observed, but were highly variable. Therefore, the clinical significance of this finding was unclear.
Cationic drugs: Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) have the potential for interaction with metformin by competing for common renal tubular transport systems. careful monitoring of patients and doses of metformin and such medications are recommended.
Other: Close monitoring of glycaemic control and metformin dose adjustments are recommended when co administered with thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. Avoid consumption of alcohol and medicinal products containing alcohol.

USE IN SPECIFIC POPULATIONS:
Pregnancy and lactation:
Pregnancy: There are no adequate and well-controlled studies in pregnant women and therefore, GALZA-Met should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.
Lactation: No studies have been conducted with the combined components of GALZA-Met. As it is not known whether vildagliptin and/or metformin hydrochloride is excreted in human milk GALZA-Met should not be administered to breast-feeding women.

ADVERSE REACTIONS:
Adverse effects:
There have been no therapeutic clinical trials conducted with GALZA-Met. However, bioequivalence of GALZA-Met with co-administered vildagliptin and metformin has been demonstrated (see Pharmacokinetic properties). The data presented here relate to the co-administration of vildagliptin and metformin, where vildagliptin has been added to metformin. There have been no studies of metformin added to vildagliptin. Rare cases of angioedema have been reported on vildagliptin at a similar rate to controls. A greater proportion of cases were reported when vildagliptin was administered in combination with an angiotensin converting enzyme inhibitor (ACE-Inhibitor). The majority of events were mild in severity and resolved with ongoing vildagliptin treatment. Rare cases of hepatic dysfunction (including hepatitis) have been reported with vildagliptin. In these cases, the patients were generally asymptomatic without clinical sequelae and liver function tests (LFTs) returned to normal after discontinuation of treatment. In data from controlled monotherapy and add-on therapy trials up to 24 weeks in duration, the incidence of ALT or AST elevations >= 3x ULN (classified as present on at least 2 consecutive measurements or at the final on-treatment visit) was 0.2%, 0.3% and 0.2% for vildagliptin 50 mg daily, vildagliptin 50 mg twice daily and all comparators, respectively.
Specific:
- Gastrointestinal
- Dermatologic
- Intravenous Site Reactions
- Anticoagulation and Hemorrhage
- Renal
- Hepatic
- Thromboembolism

OVERDOSAGE:
In the event of overdosage, appropriate supportive treatment should be initiated according to patient's clinical signs and symptoms
Vildagliptin: Vildagliptin is not dialyzable, however the major hydrolysis metabolite (LAY151) can be removed by haemodialysis.
Metformin Hydrochloride: Overdose of metformin hydrochloride has occurred Lactic acidosis has been reported in approximately 32% of metformin hydrochloride overdose cases. Metformin hydrochloride is dialyzable with a clearance of up to 170 mL/min under good haemodynamic conditions. Therefore, haemodialysis may be useful for removal of accumulated drug from patients in whom metformin hydrochloride overdosage is suspected.

INSTRUCTIONS:
Store below 30°C. Protect from heat, sunlight & moisture. Keep out of the reach of children. To be sold on the prescription of a registered medical practitioner only.

PRESENTATION:

GALZA-MET 50/500 Tablet	:	Pack of 2 x 7 tablets.
GALZA-MET 50/850 Tablet	:	Pack of 2 x 7 tablets.
GALZA-MET 50/1000 Tablet	:	Pack of 2 x 7 tablets.

ہدایات:
۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی، دھوپ اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔
صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

FOR FURTHER INFORMATION PLEASE CONTACT.

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