Gvia®

جیویا

(Sitagliptin)

(سیٹاگلپٹن) ٹیبلٹس یو۔ایس۔پی۔

Tablets U.S.P.

50mg 100mg

۵۰ ملی گرام ۱۰۰ ملی گرام

QUALITATIVE AND QUANTITATIVE COMPOSITION

Gvia® 50mg Tablets U.S.P.: Each film-coated tablet contains:
Sitagliptin Phosphate U.S.P. eq. to Sitagliptin.....50mg
Gvia® 100mg Tablets U.S.P.: Each film-coated tablet contains:
Sitagliptin Phosphate U.S.P. eq. to Sitagliptin.....100mg

DESCRIPTION: Gvia Tablets contain sitagliptin phosphate, an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme.

CLINICAL PHARMACOLOGY: Mechanism of Action: Sitagliptin is a DPP-4 inhibitor, which is believed to exert its actions 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. 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 by intracellular signaling pathways involving cyclic AMP. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. By increasing and prolonging active incretin levels, Sitagliptin increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner. Sitagliptin demonstrates selectivity for DPP-4 and does not inhibit DPP-8 or DPP-9 activity in vitro at concentrations approximating those from therapeutic doses.

Pharmacodynamics: General: In patients with type 2 diabetes, administration of sitagliptin led to inhibition of DPP-4 enzyme activity for a 24-hour period. After an oral glucose load or a meal, this DPP-4 inhibition resulted in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, decreased glucagon concentrations, and increased responsiveness of insulin release to glucose, resulting in higher C-peptide and insulin concentrations. The rise in insulin with the decrease in glucagon was associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal. Coadministration of sitagliptin and metformin had an additive effect on active GLP-1 concentrations. Sitagliptin, but not metformin, increased active GIP concentrations.

Cardiac Electrophysiology: From a randomized, placebo-controlled crossover study, it was found that at the recommended dose of 100mg, there was no effect on the QTc interval obtained at the peak plasma concentration, or at any other time during the study. Following the 800mg dose, the maximum increase in the placebo-corrected mean change in QTc from baseline was observed at 3 hours post dose and was 8.0 msec. This increase is not considered to be clinically significant. At the 800mg dose, peak sitagliptin plasma concentrations were approximately 11 times higher than the peak concentrations following a 100mg dose. **Pharmacokinetics:** After oral administration of a 100mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median Tmax) occurring 1 to 4 hours post dose. Plasma AUC of sitagliptin increased in a dose-proportional manner. Following a single oral 100mg dose to healthy volunteers, mean plasma AUC of sitagliptin was 8.52 μM.hr, Cmax was 950nM, and apparent terminal half-life (t1/2) was 12.4 hours. Plasma AUC of sitagliptin increased approximately 14% following 100mg doses at steady-state compared to the first dose.

Absorption: The absolute bioavailability of sitagliptin is approximately 87%. Because coadministra-

tion of a high-fat meal with Gvia had no effect on the pharmacokinetics.
Distribution: The mean volume of distribution at steady state following a single 100mg intravenous dose of sitagliptin to healthy subjects is approximately 198 liters. The fraction of sitagliptin reversibly bound to plasma proteins is low (38%).
Metabolism: Approximately 79% of sitagliptin is excreted unchanged in the urine with metabolism being a minor pathway of elimination. Following a [14C]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. **Excretion:** Following administration of an oral [14C]sitagliptin dose to healthy subjects, approximately 100% of the administered radioactivity was eliminated in feces (13%) or urine (87%) within one week of dosing. 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. Elimination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion.

INDICATIONS AND USAGE: For adult patients with type 2 diabetes mellitus, Sitagliptin is indicated to improve glycaemic control: **as monotherapy** • In patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance. **as dual oral therapy in combination with** • Metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control. • A sulphonylurea when diet and exercise plus maximal tolerated dose of a sulphonylurea alone do not provide adequate glycaemic control and when metformin is inappropriate due to contraindications or intolerance. • A peroxisome proliferator-activated receptor gamma (PPARγ) agonist (i.e. a thiazolidinedione) when use of a PPARγ agonist is appropriate and when diet and exercise plus the PPARγ agonist alone do not provide adequate glycaemic control. **as triple oral therapy in combination with** • A sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control. • A PPARγ agonist and metformin when use of a PPARγ agonist is appropriate and when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control. Gvia is also indicated as add-on to insulin (with or without metformin) when diet and exercise plus stable dose of insulin do not provide adequate glycaemic control. Important Limitations of Use: Sitagliptin 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.

CONTRAINDICATIONS: History of a serious hypersensitivity reaction to sitagliptin, such as anaphylaxis or angioedema.

INTERACTIONS: Digoxin: There was a slight increase in the area under the curve (AUC, 11%) and mean peak drug concentration (Cmax,18%) of digoxin with the coadministration of 100mg sitagliptin for 10 days. Patients receiving digoxin should be monitored appropriately. No dosage adjustment of digoxin or Gvia is recommended. Cyclosporine: Coadministration of a single 100mg oral dose of Gvia and a single 600mg oral dose of cyclosporine increased the AUC and Cmax of sitagliptin by approximately 29% and 68%, respectively. The renal clearance of sitagliptin was not meaningfully altered. Therefore, meaningful interactions would not be expected with other p-glycoprotein inhibitors.

USE IN SPECIFIC POPULATION: Pregnancy Category B: There are, however, no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if clearly needed. **Nursing Mothers:** It is not known whether sitagliptin is excreted in human milk. Caution should be exercised when Gvia is administered to a nursing woman. Pediatric Use: Safety and effectiveness of Gvia in pediatric patients under 18 years of age have not been established. **Geriatric Use:** This drug is known to be substantially excreted by the kidney.It may be useful to assess renal function in these patients prior to initiating dosing and periodically thereafter.

PRECAUTIONS: Pancreatitis: There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking Gvia. After initiation of Gvia, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, Gvia should promptly be discontinued and appropriate management should be ini-

tiated. **Renal Impairment:** Assessment of renal function is recommended prior to initiating Gvia and periodically thereafter. A dosage adjustment is recommended in patients with moderate or severe renal insufficiency and in patients with ESRD requiring hemodialysis or peritoneal dialysis. **Hepatic Insufficiency:** In patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), mean AUC and Cmax of sitagliptin increased approximately 21% and 13%, respectively, compared to healthy matched controls following administration of a single 100mg dose of Gvia. No dosage adjustment for Gvia is necessary for patients with mild or moderate hepatic insufficiency. There is no clinical experience in patients with severe hepatic insufficiency (Child-Pugh score >9).

Use with Medications Known to Cause Hypoglycemia: When Gvia was used in combination with a sulfonylurea or with insulin, medications known to cause hypoglycemia. Therefore, a lower dose of sulfonylurea or insulin may be required to reduce the risk of hypoglycemia.

Hypersensitivity Reactions: These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment with Gvia, with some reports occurring after the first dose. **Severe and Disabling Arthralgia:** There have been postmarketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors. Bullous Pemphigoid: Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor.

ADVERSE REACTIONS: Adverse reactions reported in ≥5% of patients treated with Gvia are: upper respiratory tract infection, nasopharyngitis and headache. In controlled clinical studies as both monotherapy and combination therapy with metformin, pioglitazone, or rosiglitazone and metformin, hypoglycemia occurs as adverse reaction. Peripheral edema, abdominal pain, nausea and diarrhea also occur. Body Mass Index (BMI): No dosage adjustment is necessary based on BMI. Gender: No dosage adjustment is necessary based on gender. Race: No dosage adjustment is necessary based on race. Geriatric: No dosage adjustment is required based solely on age. Pediatric: Studies characterizing the pharmacokinetics of sitagliptin in pediatric patients have not been performed.

DOSAGE AND ADMINISTRATION: Recommended Dosing: The recommended dose of Gvia is 100mg once daily. Gvia can be taken with or without food.

Dosage Adjustment in Patients with Moderate, Severe and End Stage Renal Disease(ESRD)	
50mg once daily	25mg once daily
Moderate CrCl >30 to <50mL/min ~Serum Cr levels [mg/dL] Men: >1.7– ≤3.0; Women: >1.5– ≤2.5	**Severe and ESRD** CrCl <30mL/min ~Serum Cr levels [mg/dL] Men: >3.0; Women: >2.5; or on dialysis

Patients with Renal Insufficiency: For patients with mild renal insufficiency (creatinine clearance [CrCl] greater than or equal to 50 mL/min, approximately corresponding to serum creatinine levels of less than or equal to 1.7 mg/dL in men and less than or equal to 1.5 mg/dL in women), no dosage adjustment for Gvia is required.

For patients with moderate renal insufficiency (CrCl greater than or equal to 30 to less than 50 mL/min, approximately corresponding to serum creatinine levels of greater than 1.7 to less than or equal to 3.0 mg/dL in men and greater than 1.5 to less than or equal to 2.5 mg/dL in women), the dose of Gvia is 50mg once daily. Caution should be used to ensure that the correct dose of Gvia is prescribed for patients with moderate (creatinine clearance ≥30 to <50 mL/min) or severe (creatinine clearance <30 mL/min) renal impairment. There have been postmarketing reports of worsening renal function, including acute renal failure, sometimes requiring dialysis. Sitagliptin was modestly removed by hemodialysis (13.5% over a 3- to 4-hour hemodialysis session starting 4 hours postdose). To achieve plasma concentrations of sitagliptin similar to those in patients with normal renal function, lower dosages are recommended in patients with moderate and severe renal insufficiency, as well as in ESRD patients requiring dialysis.

For patients with severe renal insufficiency (CrCl less than 30 mL/min, approximately corresponding to serum creatinine levels of greater than 3.0 mg/dL in men and greater than 2.5mg/dL in women) or with end-stage renal disease (ESRD) requiring hemodialysis or peritoneal dialysis, the

dose of Gvia is 25mg once daily. Gvia may be administered without regard to the timing of dialysis.
Overdosage: There is no experience with doses above 800mg in clinical studies.In Phase I multiple-dose studies, there were no dose-related clinical adverse reactions observed with Gvia with doses of up to 600mg per day for periods of up to 10 days and 400mg per day for up to 28 days. 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 dictated by the patient's clinical status. Sitagliptin is modestly dialyzable. In clinical studies, approximately 13.5% of the dose was removed over a 3- to 4-hour hemodialysis session. Prolonged hemodialysis may be considered if clinically appropriate.It is not known if sitagliptin is dialyzable by peritoneal dialysis.
Missed dose: If a dose of Sitagliptin is missed,it should be taken as soon as possible as the patient remembers. A double dose should not be taken on the same day.

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® 50mg film-coated tablets U.S.P. are available in Alu-Alu blister pack of 2x14's.
Gvia® 100mg film-coated tablets U.S.P. are available in Alu-Alu blister pack of 2x14's.

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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