Trapeze Tablets*

ٹریپیز ٹیبلٹس

COMPOSITION: *Each film coated tablet contains:*
Sitagliptin Phosphate Monohydrate eq. to Sitagliptin* 25, 50 & 100 mg, respectively.

DESCRIPTION: Trapeze tablets contain sitagliptin phosphate (molecular weight is 505.32), an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme. Sitagliptin phosphate monohydrate is described chemically as 7-[(3R)-3-amino-1-oxo-4-(2,4,5- trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-μ]pyrazine phosphate (1:1) monohydrate. The empirical formula is $C_{16}H_{15}F_6N_5O \cdot H_3PO_4 \cdot H_2O$ and the molecular weight is 523.32.

PHARMACOLOGY: *Pharmacodynamics:* 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. 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. *Pharmacokinetics:* After 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. The absolute bioavailability of sitagliptin is approximately 87%. Coadministration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics. Sitagliptin may be administered with or without food. The fraction of sitagliptin reversibly bound to plasma proteins is low (38%). Approximately 79% of sitagliptin is excreted unchanged in the urine with metabolism being a minor pathway of elimination. 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. Following administration of an oral [^{14}C] 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 100 mg 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: *Monotherapy & Combination Therapy:* Trapeze Tablets are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

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

POSSIBLE ADVERSE EFFECTS: As both monotherapy and combination therapy with metformin or pioglitazone, the overall incidence of adverse reactions, hypoglycemia, and discontinuation of therapy due to clinical adverse reactions with sitagliptin are similar to placebo. The commonly encountered side effects include hypoglycaemia, headache and upper respiratory tract infections.

DRUG INTERACTIONS: There was a slight increase in the area under the curve (AUC, 11%) and mean peak drug concentration (C_{max}, 18%) of digoxin with the co-administration of 100 mg sitagliptin for 10 days. Patients receiving digoxin should be monitored appropriately. No dosage adjustment of digoxin or sitagliptin is recommended.

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

discontinued and appropriate management should be initiated. *Use in Patients with Renal Insufficiency:* A dosage adjustment is recommended in patients with moderate or severe renal insufficiency and in patients with ESRD requiring hemodialysis or peritoneal dialysis. *Use with Medications Known to Cause Hypoglycemia:* As is typical with other antihyperglycemic agents used in combination with a sulfonylurea, when sitagliptin was used in combination with a sulfonylurea, a class of medications known to cause hypoglycemia, the incidence of hypoglycemia was increased over that of placebo Therefore, a lower dose of sulfonylurea may be required to reduce the risk of hypoglycemia. *Hypersensitivity Reactions:* There have been postmarketing reports of serious hypersensitivity reactions in patients treated with sitagliptin. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. If a hypersensitivity reaction is suspected, discontinue sitagliptin. *Pregnancy:* No adequate and well-controlled studies in pregnant women are available. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. *Lactation:* Caution should be exercised when sitagliptin is administered to a nursing woman. *Pediatric Use:* Safety and effectiveness of sitagliptin 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. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in the elderly, and it may be useful to assess renal function in these patients prior to initiating dosing and periodically thereafter.

DOSAGE & ADMINISTRATION: The recommended dose is 100 mg (2 tablets of Trapeze 50 mg) once daily. Trapeze can be taken with or without food. *Patients with Renal Insufficiency:* For patients with mild renal insufficiency (creatinine clearance [CrCl] ³50 mL/min, approximately corresponding to serum creatinine levels of ²1.7 mg/dL in men and ²1.5 mg/dL in women), no dosage adjustment for Trapeze is required. For patients with moderate renal insufficiency (CrCl ³30 to <50 mL/min, approximately corresponding to serum creatinine levels of >1.7 to ²3.0 mg/dL in men and >1.5 to ²2.5 mg/dL in women), the dose of Trapeze is 50 mg once daily. For patients with severe renal insufficiency (CrCl <30 mL/min, approximately corresponding to serum creatinine levels of >3.0 mg/dL in men and >2.5 mg/dL in women) or with end-stage renal disease (ESRD) requiring hemodialysis or peritoneal dialysis, the dose of Trapeze is 25 mg once daily. *Concomitant Use with a Sulfonylurea:* When Trapeze is used in combination with a sulfonylurea, a lower dose of sulfonylurea may be required to reduce the risk of hypoglycemia.

SPECIAL INSTRUCTIONS TO THE PHYSICIAN: *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. Sitagliptin has not been studied in combination with insulin. Sitagliptin 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 sitagliptin. *Overdosage:* 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 by hemodialysis.

STORAGE/PRECAUTIONS: Store in a cool, dry and dark place below 25 °C. Keep all medicines out of the children's reach.

PRESENTATION: Trapeze Tablets 25, 50 & 100 mg are available in packing containing 14 film coated tablets. **Scotmann Specs.*

عمومی خوراک: ڈاکٹر کی ہدایت کے مطابق۔ احتیاط: دواصرف مستند ڈاکٹر کے زیرِ ہدایت استعمال کریں۔ روشنی، نمی اور گرمی سے بچائیں۔ 25 ڈگری سینٹی گریڈ سے کم درجہ حرارت پر محفوظ کریں۔ تمام ادویات بچوں کی پہنچ سے دور رکھیں۔

Complete Medical Information available only for doctors on request.

scotmann

Manufactured by: **SCOTMANN PHARMACEUTICALS**
5-D, I-10/3 Industrial Area, Islamabad-Pakistan.