Trapeze *plus* Tablets*

ٹریپیز پلس ٹیبلٹس

COMPOSITION:

Each film coated Trapeze plus 50/500 mg Tablet contains: Sitagliptin Phosphate Monohydrate eq. to Sitagliptin*.....50 mg & Metformin HCl BP/USP.....500 mg

Each film coated Trapeze plus 50/1000 mg Tablet contains: Sitagliptin Phosphate Monohydrate eq. to Sitagliptin*...50 mg & Metformin HCl BP/USP.....1000 mg

DESCRIPTION: Trapeze plus (Sitagliptin+Metformin HCl) contains two oral antihyperglycemic agents with complementary mechanism of action to improve glycemic control with type 2 diabetes. Sitagliptin is an orally-active, potent and highly selective inhibitor of the dipeptidyl peptidase 4 (DPP-4). Chemically, it is 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-a]pyrazine phosphate (1:1) monohydrate and its molecular weight is 523.32. Its molecular formula is $C_{16}H_{15}F_6N_5O.H_3PO_4.H_2O$. Metformin HCl (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral anti-hyperglycemic agents. It has a molecular formula of $C_4H_{11}N_5.HCl$.

PHARMACOLOGY: *Mechanism of Action:* **Sitagliptin:** It 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, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). 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 increases 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. **Metformin HCl:** It is a biguanide with antihyperglycemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycemia. Metformin HCl may active via three mechanisms:

- By reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis.
- In muscle, by modestly increasing insulin sensitivity, improving peripheral glucose uptake and utilization.
- By delaying intestinal glucose absorption.

Pharmacokinetics: *Absorption:* **Sitagliptin:** The absolute bioavailability of Sitagliptin is approximately 87%. Co-administration of a high-fat meal with Sitagliptin had no effects on the pharmacokinetics of Sitagliptin. **Metformin HCl:** The absolute bioavailability of a Metformin hydrochloride 500 mg tablet given under fasting conditions is approximately 50-60%. Studies indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of Metformin, as shown by approximately 40% lower mean peak plasma concentration (Cmax), a 25% lower area under the plasma concentration versus time curve (AUC). The pharmacokinetics of Metformin HCl absorption is non-linear. *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 reversibly bound to plasma protein is low (38%). **Metformin HCl:** Metformin HCl is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin HCl partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of Metformin HCl tablets, steady state plasma concentrations of Metformin HCl are reached within 24-48 hours and are generally <1 mcg/mL. Maximum Metformin HCl plasma levels do not exceed 5mcg/mL, even at maximum doses. *Metabolism:* **Sitagliptin:** Approximately 79% of Sitagliptin is excreted unchanged in urine with metabolism being a minor pathway of elimination. **Metformin HCl:** Metformin HCl is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans), nor biliary excretion. *Excretion:* **Sitagliptin:** Sitagliptin is excreted through feces (13%) or urine (87%) within one week of dosing. Elimination of Sitagliptin occurs primarily via renal excretion and involves active tubular secretion. **Metformin HCl:** Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of Metformin HCl elimination. 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.

INDICATIONS: Trapeze plus (Sitagliptin+Metformin HCl) is indicated as:

- Initial therapy in patients with type 2 diabetes mellitus to improve glycemic control when diet and exercise do not provide adequate glycemic control.
- As an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus inadequately controlled on Metformin HCl or Sitagliptin alone or in patients already being treated with the combination of Sitagliptin and Metformin HCl.
- In triple combination with a sulphonylurea as an adjunct to diet and exercise in patients with type 2 diabetes mellitus inadequately controlled on their maximal tolerated dose of Metformin HCl and a sulphonylurea.
- In triple combination with a peroxisome proliferator-activated receptor gamma PPAR◦ agonist (thiazolidinedione) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of Metformin HCl and PPAR◦ agonist.
- In patient with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycemic control in combination with insulin.

CONTRAINDICATIONS: The combination of Sitagliptin and Metformin HCl is contraindicated in:

- Patients with type 1 diabetes
- Renal disease or renal dysfunction, e.g. as suggested by serum creatinine levels ³1.5mg/dL (females), or abnormal creatinine clearance, which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia
- Patients with known hypersensitivity to Sitagliptin, Metformin HCl or any other component of the product
- Acute or chronic metabolic acidosis, including ketoacidosis, with or without coma
- Children below 18 years of age
- Pregnancy
- Lactation

POSSIBLE ADVERSE EFFECTS: The following adverse reactions were reported with Sitagliptin/Metformin HCl combination therapy: *CNS:* Headache. *GIT:* Diarrhea, nausea, abdominal pain, vomiting, acute pancreatitis, including fatal and nonfatal hemorrhagic and necrotizing pancreatitis. *Hypersensitivity:* Angioedema, cutaneous vasculitis, exfoliative skin conditions (including Stevens-Johnson syndrome), hypersensitivity (including anaphylaxis, rash, urticaria). *Metabolic-Nutritional:* Hypoglycemia. *Respiratory:* Upper respiratory tract infection. *Miscellaneous:* Hepatic enzyme elevations.

DRUG INTERACTIONS: *Alcohol:* Hypoglycemic effects and the effects of Metformin HCl on lactic acidosis may be potentiated. Warn patients against excessive alcohol intake, acute or chronic, while receiving Sitagliptin/Metformin HCl. *Cationic drugs (e.g. amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, vancomycin):* May compete with Metformin HCl for renal tubular transport. Although such interactions remain theoretical, careful patient monitoring and dose adjustment of Sitagliptin/Metformin HCl and/or the interfering drug is recommended in patients who are taking cationic medications excreted via the proximal renal tubular secretory system. *Cimetidine:* Metformin HCl plasma levels may be increased. Metformin HCl pharmacologic effects and risk of adverse reactions may be increased. Monitor renal function closely. Dosage reduction may be needed during coadministration of cimetidine. *Cyclosporine*: Coadministration of a single oral dose of Sitagliptin 100 mg and cyclosporine 600 mg increased the AUC and Cmax of Sitagliptin, AUC and Cmax may be increased. However, the magnitude of the change is not expected to be clinically important. *Digoxin:* Digoxin AUC and Cmax may be slightly increased. These increases are not likely to be clinically important. *Drugs that produce hyperglycemia (e.g., calcium channel blockers, corticosteroids, diuretics (e.g., indomethacin thiazides), estrogens, hormonal contraceptives, isoniazid, nicotinic acid, phenothiazines, phenytoin, sympathomimetics, thyroid products):* Closely monitor patient to maintain adequate glycemic control. *Food:* Food may decrease the extent and slightly delay the absorption of Metformin HCl, as shown by decrease in Cmax and AUC, and a prolongation of tmax. Sitagliptin/Metformin HCl should be taken with food. *Furosemide:* Metformin HCl AUC and Cmax may be increased, while the AUC and Cmax of furosemide may be decreased. The renal clearance of furosemide and Metformin HCl are not changed. *Glyburide:* Glyburide AUC and Cmax may be decreased. The clinical importance of this interaction is uncertain. Monitor blood glucose and, if an interaction is suspected, adjust the glyburide dose as needed. *Meglitinides (e.g., indomethacin, nateglinide, repaglinide):* May increase risk of hypoglycemia. A lower dose of the meglitinide may be needed to reduce the risk of hypoglycemia. *Nifedipine:* Metformin HCl AUC and Cmax may be increased. *NSAIDs (e.g., indomethacin, rofecoxib):* NSAIDs may decrease glomerular filtration, increasing Metformin HCl concentrations and the risk of lactic acidosis. Use with caution. Closely monitor renal function and for lactic acidosis. Lactic acidosis is medical emergency that must be treated in a hospital setting. If an interaction is suspected, consider discontinuing the NSAID. *Sulfonylureas:* May increase risk of hypoglycemia. A lower dose of the sulfonylurea may be needed to reduce the risk of hypoglycemia.

WARNINGS: *Lactic Acidosis:* Lactic acidosis is a rare, but serious, metabolic complication that can occur due to Metformin HCl accumulation during treatment with Metformin HCl; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypo-perfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When Metformin HCl is implicated as the cause of lactic acidosis, Metformin HCl plasma levels >5 µg/mL are generally found. Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking Metformin HCl, the drug should be discontinued immediately and general supportive measures promptly instituted. 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 HCl. Such management often results

in prompt reversal of symptoms and recovery. *Pancreatitis:* There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking Sitagliptin+Metformin HCl combination. After initiation of Sitagliptin+Metformin HCl combination, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, Sitagliptin+Metformin HCl combination should promptly be discontinued and appropriate management should be initiated. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using Sitagliptin+Metformin HCl combination. *Impaired Hepatic Function:* Since impaired hepatic function has been associated with some cases of lactic acidosis, Sitagliptin+Metformin HCl combination should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. *Assessment of Renal Function:* Metformin HCl and Sitagliptin are known to be substantially excreted by the kidney. The risk of Metformin HCl accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive Sitagliptin+Metformin HCl combination. In the elderly, Sitagliptin+Metformin HCl combination should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging can be associated with reduced renal function. There have been postmarketing reports of worsening renal function, including acute renal failure, sometimes requiring dialysis. Before initiation of therapy with Sitagliptin+Metformin HCl combination and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, particularly in elderly patients, renal function should be assessed more frequently and Sitagliptin+Metformin HCl combination discontinued if evidence of renal impairment is present. *Vitamin B12 Levels:* In controlled clinical trials of Metformin HCl of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B12 levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of Metformin HCl or Vitamin B12 supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on Sitagliptin+Metformin HCl combination and any apparent abnormalities should be appropriately investigated and managed. 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 is known to potentiate the effect of Metformin HCl on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving Sitagliptin+Metformin HCl combination. *Surgical Procedures*: Use of Sitagliptin+Metformin HCl combination 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 Sitagliptin+Metformin HCl combination 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 HCl levels. If acidosis of either form occurs, Sitagliptin+Metformin HCl combination must be stopped immediately and other appropriate corrective measures initiated. *Use with Medications Known to Cause Hypoglycemia:* When Sitagliptin was used in combination with a sulfonylurea or with insulin, medications known to cause hypoglycemia, the incidence of hypoglycemia was increased over that of placebo used in combination with a sulfonylurea or with insulin. 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. *Concomitant Medications Affecting Renal Function or Metformin HCl Disposition:* Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of Metformin HCl, 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 HCl. Therefore, in patients in whom any such study is planned, Sitagliptin+Metformin HCl combination should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal. *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 Sitagliptin+Metformin HCl combination 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 Sitagliptin+Metformin HCl combination and temporarily administer insulin. Sitagliptin+Metformin HCl combination may be reinstituted after the acute episode is resolved. *Hypersensitivity Reactions:* There have been postmarketing reports of serious hypersensitivity reactions in patients treated with Sitagliptin, one of the components of Sitagliptin+Metformin HCl combination. 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 Sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue Sitagliptin+Metformin HCl combination, assess for other potential causes for the event, and institute alternative treatment for diabetes. *Macrovascular Outcomes:* There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Sitagliptin+Metformin HCl combination or any other anti-diabetic drug. *Nursing Mothers:* No studies in lactating animals have been conducted with the combined components of Sitagliptin+Metformin HCl combination. In studies performed with the individual components, both Sitagliptin and Metformin HCl are secreted in the milk of lactating rats. It is not known whether Sitagliptin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Sitagliptin+Metformin HCl combination is administered to a nursing woman. *Pediatric Use:* Safety and effectiveness of Sitagliptin+Metformin HCl combination in pediatric patients under 18 years have not been established. *Geriatric Use:* Because Sitagliptin and Metformin HCl are substantially excreted by the kidney, and because aging can be associated with reduced renal function, Sitagliptin+Metformin HCl combination should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function.

DOSAGE & ADMINISTRATION: The dosage of Trapeze plus (Sitagliptin+Metformin HCl) should be individualized on the basis of patient's current regimen, effectiveness and tolerability while not exceeding the maximum recommended daily dose of 100mg Sitagliptin. It should be given twice daily with meals, with gradual dose escalation, to reduce the gastrointestinal (GI) side effects associated with Metformin HCl. *As Initial Therapy:* For patients with type 2 diabetes mellitus, whose hyperglycemia is inadequately controlled with diet and exercise alone, the recommended starting dose Trapeze plus (Sitagliptin+Metformin HCl) is 50 mg of Sitagliptin+500 mg of Metformin HCl twice daily. Patients may be titrated up to 50 mg of Sitagliptin+1000 mg of Metformin HCl twice daily. *For patients inadequately controlled on Metformin HCl monotherapy:* The usual starting dose of Trapeze plus (Sitagliptin+Metformin HCl) should provide Sitagliptin dosed as 50 mg twice daily (100 mg total daily dose), plus Metformin HCl dose already being taken. *For patients inadequately controlled on Sitagliptin monotherapy:* The usual starting dose of Trapeze plus (Sitagliptin+Metformin HCl) is 50 mg Sitagliptin+500 mg Metformin HCl twice daily. Patients may be titrated up to 50 mg Sitagliptin+1000 mg of Metformin HCl twice daily. *For patients switching from Sitagliptin co-administered with Metformin HCl:* For patients switching from co-administration of Sitagliptin and Metformin HCl, Trapeze plus (Sitagliptin+Metformin HCl) may be initiated at the dose of Sitagliptin+1000 mg Metformin HCl already being taken. *For patients inadequately controlled on dual combination therapy with any two of following three anti-hyperglycemic agent: Sitagliptin, Metformin HCl or PPAR◦ agonist (thiazolidinedione):* The usual starting dose of Trapeze plus (Sitagliptin+Metformin HCl) should provide Sitagliptin dosed as 50 mg twice daily (100 mg total daily dose). In determining the starting dose of Metformin HCl component, the patient level of glycemic control and current dose (if any) of Metformin HCl should be considered. *For patients inadequately controlled on dual combination therapy with any two of following three anti-hyperglycemic agent: Sitagliptin, Metformin HCl or sulphonylurea:* The usual starting dose of Trapeze plus (Sitagliptin+Metformin HCl) should provide Sitagliptin dosed as 50 mg twice daily (100 mg total daily dose). In determining the starting dose of Metformin HCl component, the patient level of glycemic control and current dose (if any) of Metformin HCl should be considered. *For patients inadequately controlled on dual combination therapy with any two of following three anti-hyperglycemic agent: Sitagliptin, Metformin HCl or insulin:* The usual starting dose of Trapeze plus (Sitagliptin+Metformin HCl) should provide Sitagliptin dosed as 50 mg twice daily (100 mg total daily dose). In determining the starting dose of Metformin HCl component, the patient level of glycemic control and current dose (if any) of Metformin HCl should be considered.

SPECIAL INSTRUCTIONS TO THE PHYSICIAN: *Overdosage:* **Sitagliptin:** *I*n 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 obtain an electrocardiogram) and institute supportive as dictated by the patient's clinical status. Sitagliptin is modestly dialyzable. Prolonged hemodialysis may be considered if clinically appropriate. It is not known if Sitagliptin is dialyzable by peritoneal dialysis. **Metformin HCl:** In case of Metformin HCl overdose (greater than 50g), hypoglycemia was reported in approximately 10% of cases but no casual association with Metformin HCl has been established. Metformin HCl is dialyzable with a clearance of up to 170mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom Metformin HCl over dosage is suspected.

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

PRESENTATION: Trapeze plus Tablets 50/500 mg & 50/1000 mg are available in 10 film coated tablets, respectively.
*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

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