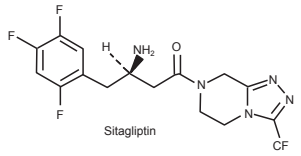
Trevia™

[SITAGLIPTIN TABLETS USP]

50mg & 100mg Tablets

DESCRIPTION

TREVIA (Sitagliptin) is an orally-active, potent and highly selective inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme used for the treatment of type 2 diabetes. 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. Its molecular formula is $C_{16}H_{15}F_6N_5O \cdot H_3PO_4 \cdot H_2O$ and the structural formula is:



Sitagliptin

Trevia Tablets 50mg is available as peach orange colored round shaped, biconvex film coated tablet, plain on both sides.
Trevia Tablets 100mg is available as peach orange colored, round shaped, biconvex film coated tablet, bisect line on one side and plain on the other side.
The scoring on the tablet is non-functional

QUALITATIVE & QUANTITATIVE COMPOSITION

TREVIA (Sitagliptin) is available for oral administration as:

1. TREVIA Tablets 50mg
   Each film-coated tablet contains:
   Sitagliptin phosphate (as monohydrate) USP equivalent to Sitagliptin... 50mg

2. TREVIA Tablets 100mg
   Each film-coated tablet contains:
   Sitagliptin phosphate (as monohydrate) USP equivalent to Sitagliptin... 100mg

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, 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 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.

Pharmacokinetics

Absorption

Following oral administration of a 100mg dose, sitagliptin absorbs rapidly with peak plasma concentration (median T_{max}) occurring 1 to 4 hours post-dose, mean plasma AUC of sitagliptin is 8.52 μm•hr, with C_{max} 950nM. The absolute bioavailability of sitagliptin is approximately 87%. Plasma AUC of sitagliptin increased in a dose-proportional manner.

Distribution

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 proteins is low (38%).

Metabolism & Excretion

Sitagliptin is primarily eliminated unchanged in urine (approximately 79%), and metabolism is a minor pathway. Following administration of an oral [^{14}C] sitagliptin dose, approximately 100% of the administered radioactivity eliminate in feces (13%) or urine (87%) within one week of dosing. The apparent terminal $t_{1/2}$ following a 100mg oral dose of sitagliptin is approximately 12.4 hours and renal clearance is approximately 350mL/min.

Special Populations

Renal Insufficiency

Patients with mild renal insufficiency did not have a clinically meaningful increase in the plasma concentration of sitagliptin. The plasma AUC of sitagliptin increases approximately 2-fold in patients with moderate renal insufficiency, and an approximately 4-fold in patients with severe renal insufficiency and in patients with ESRD on hemodialysis.

Hepatic Insufficiency

There is no clinical experience in patients with severe hepatic insufficiency (Child-Pugh score> 9). However, because sitagliptin is primarily renally eliminated, severe hepatic insufficiency is not expected to affect the pharmacokinetics of sitagliptin.

Elderly

Elderly subjects (65 to 80 years) had approximately 19% higher plasma concentrations of sitagliptin compared to younger subjects.

THERAPEUTIC INDICATIONS

TREVIA (Sitagliptin) is indicated in patients with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycemic control as:

- Monotherapy
  In patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance.
- Dual Therapy
  In combination with metformin HCl or with a sulphonylurea or with a PPARγ agonist (i.e.,thiazolidinediones) when the treatment with the single agent alone, with diet and exercise, does not provide adequate glycemic control.
- Triple Therapy
  In combination with metformin HCl and a sulphonylurea or with metformin HCl and a PPARγ (i.e.,thiazolidinediones) when dual therapy with these agents, with diet and exercise, does not provide adequate glycemic control.
- Add on to Insulin
  (With or without metformin) when diet and exercise plus stable dose of insulin do not provide adequate glycaemic control.

DOSAGE AND ADMINISTRATION

The recommended dose of TREVIA (Sitagliptin) is 100mg once daily as monotherapy or as combination therapy with metformin HCl, a sulphonylurea, insulin (with or without metformin HCl), a PPARγ agonist (i.e., thiazolidinediones), metformin HCl plus a sulphonylurea, or metformin HCl plus a PPARγ agonist (i.e., thiazolidinediones).
When TREVIA (Sitagliptin) is used in combination with a sulphonylurea or with insulin, a lower dose of sulphonylurea or insulin may be considered to reduce the risk of sulphonylurea or insulin-induced hypoglycemia.

Co administration of a high-fat meal with TREVIA (Sitagliptin) had no effect on the pharmacokinetics, TREVIA (Sitagliptin) may be administered with or without food.

If a dose of TREVIA (Sitagliptin) is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day.

Special Populations

Renal Insufficiency

For patients with mild renal insufficiency (creatinine clearance [Cl_{Cr}] ≥ 50mL/min, approximately corresponding to serum creatinine levels of ≤1.7mg/dL in men and ≤1.5mg/dL in women), no dosage adjustment for sitagliptin is required.
For patients with moderate renal insufficiency (Cl_{Cr} ≤30 to <50 mL/min, approximately corresponding to serum creatinine levels of >1.7 to ≤3.0mg/dL in men and >1.5 to ≤2.5 mg/dL in women), the dose of sitagliptin is 50 mg once daily.
For patients with severe renal insufficiency (Cl_{Cr}≤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 sitagliptin is 25mg once daily. Sitagliptin may be administered without regard to the timing of hemodialysis.

Elderly

No dose adjustment is required based on age.

Pediatric Use

Safety and effectiveness of Sitagliptin in pediatric patients under 18 years of age have not been established.

ADVERSE REACTIONS

Monotherapy

Not known: Hypersensitivity reactions including anaphylactic responses, interstitial lung disease, vomiting, acute pancreatitis, fatal and non-fatal hemorrhagic, necrotizing pancreatitis, angioedema, rash, urticaria, cutaneous vasculitis, exfoliative skin conditions including Stevens-Johnson syndrome, bullous pemphigoid, arthralgia, myalgia, back pain, arthropathy, impaired renal function and acute renal failure.
Common: Hypoglycaemia, headache, upper respiratory-tract infections and nasopharyngitis.
Uncommon: Dizziness, constipation and pruritus.

Combination with other anti-diabetic medicinal product

Adverse reaction reported when Sitagliptin is used with other anti-diabetic

medicinal products includes hypoglycemia (very common with the combination of sulphonylurea and metformin), influenza (common with insulin (with or without metformin)), nausea and vomiting (common with metformin), flatulence (common with metformin or pioglitazone), constipation (common with the combination of sulphonylurea and metformin), peripheral edema (common with pioglitazone or the combination of pioglitazone and metformin), somnolence and diarrhea (uncommon with metformin), and dry mouth (uncommon with insulin (with or without metformin)).

TECOS Cardiovascular Safety Study
The Trial Evaluating Cardiovascular Outcomes with sitagliptin (TECOS) included patients treated with sitagliptin, 100 mg daily (or 50 mg daily if the baseline eGFR was ≥ 30 and < 50 mL/min/1.73 m^2), and patients treated with placebo in the intention-to-treat population. Both treatments were added to usual care targeting regional standards for HbA1c and CV risk factors. The overall incidence of serious adverse events in patients receiving sitagliptin was similar to that in patients receiving placebo.

In the intention-to-treat population, among patients who were using insulin and/or a sulfonylurea at baseline, the incidence of severe hypoglycemia was 2.7% in sitagliptin-treated patients and 2.5% in placebo-treated patients; among patients who were not using insulin and/or a sulfonylurea at baseline, the incidence of severe hypoglycemia was 1.0% in sitagliptin-treated patients and 0.7% in placebo-treated patients. The incidence of adjudication-confirmed pancreatitis events was 0.3% in sitagliptin-treated patients and 0.2% in placebo-treated patients.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to Getz Pharma's Pharmacovigilance Section, please contact at dsafety@getzpharma.com.

CONTRAINDICATIONS
Sitagliptin is contraindicated in:
- Patients with known hypersensitivity to sitagliptin or any of the components of the product.
- Patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.
- Children below 18 years of age.

Pregnancy
The safety of sitagliptin in pregnant women is not known. Sitagliptin, like other oral antihyperglycemic agents, is not recommended for use in pregnancy.

Nursing Mother
It is not known whether sitagliptin is excreted in human milk. Because many drugs are excreted in human milk, sitagliptin should not be administered during nursing.

Fertility
Animal data do not suggest an effect of treatment with sitagliptin on male and female fertility. Human data are lacking.

PRECAUTIONS
- Pancreatitis
  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.
- Hypoglycemia
  When sitagliptin is used in combination with a sulphonylurea or with insulin, medications known to cause hypoglycemia, the incidence of hypoglycemia increases when used in combination with a sulphonylurea or with insulin. Therefore, a lower dose of sulphonylurea or insulin may be required to reduce the risk of hypoglycemia.
- Hypersensitivity reactions
  Serious hypersensitivity reactions in patients treated with sitagliptin have been reported. 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 some reports occurring after the first dose. If a hypersensitivity reaction is suspected, Sitagliptin should be discontinued. Other potential causes for the event should be assessed, and alternative treatment for diabetes initiated.
- Bullous pemphigoid
  If bullous pemphigoid is suspected, Sitagliptin should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

DRUG INTERACTIONS
Effects of other medicinal products on Sitagliptin
Interactions by co-administered medicinal products is low. Potent CYP3A4 inhibitors (i.e. ketoconazole, itraconazole, ritonavir, clarithromycin) could alter the pharmacokinetics of sitagliptin in patients with severe renal impairment or ESRD. The effect of potent CYP3A4 inhibitors in the setting of renal impairment has not been assessed.
Sitagliptin is a substrate for p-glycoprotein and organic anion transporter-3 (OAT3). OAT3 mediated transport of sitagliptin was inhibited by probenecid, although the risk of clinically meaningful interactions is considered to be low. Concomitant administration of OAT3 inhibitors has not been evaluated.

Metformin
Co-administration of multiple twice-daily doses of 1,000 mg metformin with 50 mg sitagliptin did not meaningfully alter the pharmacokinetics of sitagliptin in patients with type 2 diabetes.

Ciclosporin
Co-administration of a single 100 mg oral dose of sitagliptin and a single 600 mg oral dose of ciclosporin increased the AUC and C_{max} of sitagliptin by approximately 29% and 68%, respectively. These changes in sitagliptin pharmacokinetics were not considered to be clinically meaningful. The renal clearance of sitagliptin was not meaningfully altered. Therefore, meaningful interactions would not be expected with other p-glycoprotein inhibitors.

Digoxin
Sitagliptin has a small effect on plasma digoxin concentrations. No dosage adjustment of digoxin is recommended. However, patients at risk of digoxin toxicity should be monitored for this when sitagliptin and digoxin are administered concomitantly.

CYP450 Isoenzymes
Sitagliptin did not meaningfully alter the pharmacokinetics of metformin, glyburide, simvastatin, rosiglitazone, warfarin, or oral contraceptives and a low propensity for causing interactions with substrates of CYP3A4, CYP2C8, CYP2C9, and organic cationic transporter (OCT). Sitagliptin may be a mild inhibitor of p-glycoprotein.

OVERDOSAGE
During controlled clinical trials in healthy subjects, single doses of up to 800 mg sitagliptin were administered. Minimal increases in QTc, not considered to be clinically relevant, were observed in one study at a dose of 800 mg sitagliptin. There is no experience with doses above 800 mg in clinical studies. In Phase I multiple-dose studies, there were no dose-related clinical adverse reactions observed with sitagliptin with doses of up to 600 mg per day for periods of up to 10 days and 400 mg per day for periods of 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. Prolonged hemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialyzable by peritoneal dialysis.

STORAGE
Do not store above 30ºC.
Protect from sunlight & moisture.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
TREVIA (Sitagliptin) Tablets 50mg are available in blister pack of 14's and 35's.
TREVIA (Sitagliptin) Tablets 100mg are available in blister pack of 14's and 35's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Getz pharma (PVT) LIMITED
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