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-{3-[3(R)-3-amino-4-[2,4,5-trifluorophenyl]butanoyl]-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-d]pyrazinanemonophosphate monohydrate. Its molecular formula is C<sub>31</sub>H<sub>27</sub>N<sub>5</sub>O<sub>7</sub>F<sub>9</sub>P<sub>1</sub> and the structural formula is:

![Structural formula of Sitagliptin](image)

QUALITATIVE & QUANTITATIVE COMPOSITION
TREVIA (Sitagliptin) is available for oral administration as:

1. TREVIA Tablets 25mg
   Each film-coated tablet contains:
   - Sitagliptin phosphate monohydrate equivalent to Sitagliptin 25mg

2. TREVIA Tablets 50mg
   Each film-coated tablet contains:
   - Sitagliptin phosphate monohydrate equivalent to Sitagliptin 50mg

3. TREVIA Tablets 100mg
   Each film-coated tablet contains:
   - Sitagliptin phosphate monohydrate 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 (cAMP). 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<sub>max</sub>) occurring 1 to 4 hours postdose, mean plasma AUC of sitagliptin is 9.52 μM/hr, with C<sub>max</sub> 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%) with metabolism being a minor pathway of elimination. Following administration of an oral [14C] sitagliptin dose, approximately 100% of the administered radioactivity eliminate in feces (13%) or urine (87%) within one week of dosing. The apparent terminal t1/2 following a 100mg oral dose of sitagliptin is approximately 12.4 hours and renal clearance is approximately 350mL/min.

Special Populations
Renal Impairment
Patients with mild renal impairment 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 impairment, and an approximately 4-fold in patients with severe renal impairment and in patients with ESRD on hemodialysis.

Hepatic Impairment
There is no clinical experience in patients with severe hepatic impairment (Child-Pugh score > 9). However, because sitagliptin is primarily renally eliminated, severe hepatic impairment 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
- Dual Therapy
in combination with a sulphonylurea or insulin-induced hypoglycemia.

- Triple Therapy
in combination with metformin HCI or with a thiazolidinediones (i.e., pioglitazone, rosiglitazone)

Common: Nausea.

Very common: Hypoglycemia.

Common: Hypoglycemia, flatulence and peripheral edema.

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 PPAR<gamma> agonist (i.e., thiazolidinediones), metformin HCl plus a sulphonylurea, or metformin HCl plus a PPAR<gamma> 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.

OVERDOSAGE
There is no specific treatment for an overdose of TREVIA (Sitagliptin). In the event of an overdose, the patient should be treated symptomatically. ECG monitoring should be performed and blood glucose levels should be monitored. If required, treatment with insulin or intravenous dextrose may be administered. Hemodialysis is not expected to be effective in reversing sitagliptin accumulation.

HOW SUPPLIED
TREVIA (Sitagliptin) Tablets 25mg are available in blister packs of 14’s.

Store at 25°C (77°F) excursions permitted between 15-30°C (59-86°F).

PROTECT FROM SUNLIGHT & MOISTURE.

Further instructions about the use of this product are available in the patient information leaflet which is supplied with each pack.

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Special Populations

Renal Impairment
For patients with mild renal impairment (creatinine clearance (CrCl) ≥ 50 mL/min, approximately corresponding to serum creatinine levels of <1.7 mg/dL in men and <1.5 mg/dL in women), no dosage adjustment for sitagliptin is required.
For patients with moderate renal impairment (CrCl ≥ 30 to <50 mL/min, approximately corresponding to serum creatinine levels of >1.7 to <3.0 mg/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 impairment (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 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.

ADVERSE REACTIONS

Monotherapy
Upper respiratory-tract infections, headache and nasopharyngitis.

Sitagliptin with Metformin HCI

Sitagliptin with Sulphonylurea
Common: Hypoglycemia.

Sitagliptin with Pioglitazone
Common: Hypoglycemia, flatulence and peripheral edema.

Sitagliptin with Sulphonylurea and Metformin HCI

Sitagliptin with a Rosiglitazone and Metformin HCI
Common: Hypoglycemia, headache, diarrhea, vomiting and peripheral edema.

Sitagliptin with Insulin
Common: Influenza, hypoglycemia and headache. Uncommon: Dry mouth and constipation.

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.

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.

Drug Interactions

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.

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. Prolonged hemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialyzable by peritoneal dialysis.

STORAGE

Store at 25°C (Excursions permitted between 15°C - 30°C). Protect from sunlight & moisture. The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED

TREVIA (Sitagliptin) Tablets 25mg are available in blister pack of 14’s.
TREVIA (Sitagliptin) Tablets 50mg are available in blister pack of 14’s.
TREVIA (Sitagliptin) Tablets 100mg are available in blister pack of 14’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.