

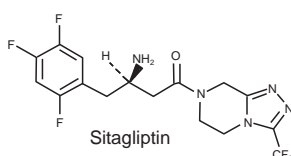
# Trevia™

[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:



### 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  $8.52 \mu\text{m} \cdot \text{hr}$ , 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 [ $^{14}\text{C}$ ] 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
- Dual Therapy  
In combination with metformin HCl or with a sulphonylurea or with a PPAR $\gamma$  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 PPAR $\gamma$  (i.e., thiazolidinediones) when dual therapy with these agents, with diet and exercise, does not provide adequate glycemic control.
- Combination with Insulin.

### 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.

### Special Populations

#### Renal Insufficiency

For patients with mild renal insufficiency (creatinine clearance [ $Cl_{cr}$ ]  $\geq 50$ mL/min, approximately corresponding to serum creatinine levels of  $\leq 1.7$ mg/dL in men and  $\leq 1.5$ mg/dL in women), no dosage adjustment for sitagliptin is required. For patients with moderate renal insufficiency ( $Cl_{cr}$   $\geq 30$  to  $< 50$  mL/min, approximately corresponding to serum creatinine levels of  $> 1.7$  to  $\leq 3.0$ mg/dL in men and  $> 1.5$  to  $\leq 2.5$  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.

#### **ADVERSE REACTIONS**

##### **Monotherapy**

Upper respiratory-tract infections, headache and nasopharyngitis.

##### **Sitagliptin with Metformin HCl**

Common: Nausea.

Uncommon: Somnolence, diarrhea, upper abdominal pain and blood glucose decreased.

##### **Sitagliptin with Sulphonylurea**

Common: Hypoglycemia.

##### **Sitagliptin with Pioglitazone**

Common: Hypoglycemia, flatulence and peripheral edema.

##### **Sitagliptin with Sulphonylurea and Metformin HCl**

Very common: Hypoglycemia.

Common: Constipation.

##### **Sitagliptin with a Rosiglitazone and Metformin HCl**

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**

Do not store above 30°C.

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.



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