SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF DRUG PRODUCT

Trevia (Sitagliptin) Tablets 100mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:
Sitagliptin phosphate (as monohydrate) USP equivalent to Sitagliptin …… 50mg

3. PHARMACEUTICAL FORM

Peach orange colored, round shaped biconvex film-coated tablet, plain on both sides.

4. CLINICAL PARTICULARS

4.1 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 or with a sulfonylurea or with a PPARγ agonist (i.e., thiazolidonediones) when the treatment with the single agent alone, with diet and exercise, does not provide adequate glycemic control.
- *Triple therapy*
  In combination with metformin and a sulfonylurea or with metformin and a PPARγ (i.e.,thiazolidonediones) when dual therapy with these agents, with diet and exercise, does not provide adequate glycemic control.
- *Combination with Insulin*

4.2 DOSAGE AND ADMINISTRATION

The recommended dose of Trevia (Sitagliptin) is 100mg once daily as monotherapy or as combination therapy with metformin, a sulfonylurea, insulin (with or without metformin), a PPARγ agonist (i.e., thiazolidonediones), metformin plus a sulfonylurea, or metformin plus a PPARγ agonist (i.e., thiazolidonediones).
When Trevia (Sitagliptin) is used in combination with a sulfonylurea or with insulin, a lower dose of sulfonylurea or insulin may be considered to reduce the risk of sulfonylurea 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 Population

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 $\geq$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 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.

4.3 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.

4.4 Special warnings and special precautions for use

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 sulfonylurea or with insulin, medications known to cause hypoglycemia, the incidence of hypoglycemia increases when used in combination with a sulfonylurea or with insulin. Therefore, a lower dose of sulfonylurea or insulin may be required to reduce the risk of hypoglycemia.

4.5 Drug Interaction

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.

4.6 Pregnancy and Lactation

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 Mothers:
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.

4.7 Undesirable effects

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.

Rare: Colonic obstruction, fecal impaction, urinary retention.

4.8 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.

5. *PHARMACOLOGICAL PROPERTIES*

5.1 Pharmacodynamic properties

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.

5.2 Pharmacokinetic Properties

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.

5.3 Preclinical safety data

Renal and liver toxicity were observed in rodents at systemic exposure values 58 times the human exposure level, while the no-effect level was found at 19 times the human exposure level. Incisor teeth abnormalities were observed in rats at exposure levels 67 times the clinical exposure level; the no-effect level for this finding was 58-fold based on the 14-weekrat study. The relevance of these findings for humans is unknown. Transient treatment-related physical signs, some of which suggest neural toxicity, such as open-mouth breathing, salivation, white foamy emesis, ataxia, trembling, decreased activity, and/or hunched posture were observed in dogs at exposure levels approximately 23 times the clinical exposure level. In addition, very slight to slight skeletal muscle degeneration was also observed histologically at doses resulting in systemic exposure levels of approximately23 times the human exposure level. A no-effect level for these findings was found at an exposure 6-fold the clinical exposure level.
Sitagliptin has not been demonstrated to be genotoxic in preclinical studies. Sitagliptin was not carcinogenic in mice. In rats, there was an increased incidence of hepatic adenomas and carcinomas at systemic exposure levels 58 times the human exposure level. Since hepatotoxicity has been shown to correlate with induction of hepatic neoplasia in rats, this increased incidence of hepatic tumours in rats was likely secondary to chronic hepatic toxicity at this high dose. Because of the high safety margin (19-fold at this no-effect level), these neoplastic changes are not considered relevant for the situation in humans.
No adverse effects upon fertility were observed in male and female rats given Sitagliptin prior to and throughout mating.
In a pre-/postnatal development study performed in rats Sitagliptin showed no adverse effects.
Reproductive toxicity studies showed a slight treatment-related increased incidence of foetal rib malformations (absent, hypoplastic and wavy ribs) in the offspring of rats at systemic exposure levels more than 29 times the human exposure levels. Maternal toxicity was seen in rabbits at more than 29 times the human exposure levels. Because of the high safety margins, these findings do not suggest a relevant risk for human reproduction.
Sitagliptin is secreted in considerable amounts into the milk of lactating rats (milk/plasma ratio: 4:1).

6. *PHARMACEUTICAL PARTICULARS*

6.1 List of Excipients

Dibasic Calcium Phosphate Anhydrous, Microcrystalline Cellulose (Avicel PH 102), Croscarmellose Sodium, Pharmacoat 606 (H.P.M.C), Colloidal Anhydrous Silica (Aerosil 200), Sodium Stearyl Fumarate, Methocel E-5 (HPMC 5CPS), Magnesium Stearate, Macrogol (P.E.G. 6000), Brown Dry mix shade O/S (1546/2840), Titanium Dioxide, Purified Talc & Purified Water.

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

3 Years
The expiration date refers to the product correctly stored in the required conditions.

6.4 Special precautions for storage

Do not store above 30°C.
Protect from sunlight & moisture.

6.5 Nature and contents of container

Trevia (Sitagliptin) Tablets are available in pack size of 5 x 7's in a unit carton along with the patient

information leaflet. **6.6 Instructions for use/handling**

- Keep out of reach of children.
- To be sold on prescription of a registered medical practitioner only.

7. *APPLICANT/HOLDER OF CERTIFICATE OF PRODUCT REGISTRATION*

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