SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medical Product

1.1 Product Name:

Sitapril 25/50/100 (Sitagliptin Tablets USP 25 mg/ 50mg/ 100 mg)

1.2 Strength:

Sitapril 25 (Sitagliptin Tablets USP 25 mg)
Each film coated tablet contains:
Sitagliptin Phosphate Monohydrate USP
equivalent to Sitagliptin (25 mg)
- Colour: Red Iron Oxide, Yellow Iron Oxide & Titanium Dioxide
- Excipients.....q.s.

Sitapril 50 (Sitagliptin Tablets USP 50mg)
Each film coated tablet contains:
Sitagliptin Phosphate Monohydrate USP
equivalent to Sitagliptin (50 mg)
- Colour: Red Iron Oxide, Yellow Iron Oxide & Titanium Dioxide
- Excipients.....q.s.

Sitapril 100 (Sitagliptin Tablets USP 100 mg)
Each film coated tablet contains:
Sitagliptin Phosphate Monohydrate USP
equivalent to Sitagliptin (100 mg)
- Colour: Red Iron Oxide, Yellow Iron Oxide & Titanium Dioxide
- Excipients.....q.s.

1.3 Pharmaceutical Dosage Form: Oral Tablets

2. Qualitative & Quantitative Composition:

Sitapril 25 (Sitagliptin Tablets USP 25 mg)
Each film coated tablet contains:
Sitagliptin Phosphate Monohydrate USP
equivalent to Sitagliptin (25 mg)
- Colour: Red Iron Oxide, Yellow Iron Oxide & Titanium Dioxide (Instacoat Aqua II A02G10250 Peach)
- Excipients.....q.s.

Sitapril 50 (Sitagliptin Tablets USP 50mg)
Each film coated tablet contains:
Sitagliptin Phosphate Monohydrate USP
equivalent to Sitagliptin (50 mg)
- Colour: Red Iron Oxide, Yellow Iron Oxide & Titanium Dioxide (Instacoat Aqua II A02G10249 Beige)
- Excipients.....q.s.

Sitapril 100 (Sitagliptin Tablets USP 100 mg)
Each film coated tablet contains:
Sitagliptin Phosphate Monohydrate USP
equivalent to Sitagliptin (100 mg)
- Colour: Red Iron Oxide, Yellow Iron Oxide & Titanium Dioxide (Instacoat Aqua II A02G10251 Beige)
- Excipients.....q.s.

For a full list of excipients, see section 6.1 of SmPC

3. Pharmaceutical Form:

Oral Tablets
Sitapril 25 (Sitagliptin Tablets USP 25 mg) :
Pink colored, round, film coated tablets debossed ‘ST1’ on one side and plain on other side

Sitapril 50 (Sitagliptin Tablets USP 50 mg) :
Light beige colored, round, film coated tablets debossed ‘ST2’ on one side and plain on other side.

Sitapril 100 (Sitagliptin Tablets USP 100 mg):
Beige colored, round, film coated tablets debossed ‘ST3’ on one side and plain on other side.

4. Clinical Particulars

4.1 Therapeutic Indications:

Sitagliptin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Limitations of Use

Sitagliptin should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

Sitagliptin has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using Sitagliptin.

4.2 Posology and Method of administration:

Recommended Dosing

The recommended dose of Sitagliptin is 100 mg once daily. Sitagliptin can be taker
without food.

Recommendations for use in Renal Impairment

When considering the use of sitagliptin in combination with another anti-diabetic m
product, its conditions for use in patients with renal impairment should be checked.

For patients with mild renal impairment (glomerular filtration rate [GFR] ≥ 60 to <
min), no dose adjustment is required.

For patients with moderate renal impairment (GFR ≥ 45 to < 60 mL/min), no
adjustment is required.

For patients with moderate renal impairment (GFR ≥ 30 to < 45 mL/min), the
Januvia is 50 mg once daily.

For patients with severe renal impairment (GFR ≥ 15 to <30 mL/min) or with en
renal disease (ESRD) (GFR < 15 mL/min), including those requiring haemodia
peritoneal dialysis, the dose of Januvia is 25 mg once daily. Treatment r
administered without regard to the timing of dialysis.

Because there is a dosage adjustment based upon renal function, assessment
function is recommended prior to initiation of Januvia and periodically thereafter.

Hepatic impairment

No dose adjustment is necessary for patients with mild to moderate hepatic impa
Sitapril has not been studied in patients with severe hepatic impairment and care
be exercised (see section 5.2).

However, because sitagliptin is primarily renally eliminated, severe hepatic impair
not expected to affect the pharmacokinetics of sitagliptin.

Elderly

No dose adjustment is necessary based on age.

Pediatric Use

Sitagliptin should not be used in children and adolescents 10 to 17 years of age b
of insufficient efficacy. Sitagliptin has not been studied in paediatric patients ur
years of age.

4.3 Contraindications:

History of a serious hypersensitivity reaction to sitagliptin, such as anaphyl
angioedema.

4.4 Special warning and precautions for use:

General

Januvia should not be used in patients with type 1 diabetes or for the treatment of ketoacidosis.

Acute pancreatitis

Use of DPP-4 inhibitors has been associated with a risk of developing acute panc Patients should be informed of the characteristic symptom of acute pancreatitis: pe severe abdominal pain. Resolution of pancreatitis has been observed after discont of sitagliptin (with or without supportive treatment), but very rare cases of necrot haemorrhagic pancreatitis and/or death have been reported. If pancreatitis is sus Sitapril and other potentially suspect medicinal products should be discontinued; pancreatitis is confirmed, Sitapril should not be restarted. Caution should be exer patients with a history of pancreatitis.

Heart Failure

An association between dipeptidyl peptidase-4 (DPP-4) inhibitor treatment an failure has been observed in cardiovascular outcomes trials for two other member DPP-4 inhibitor class. These trials evaluated patients with type 2 diabetes melli atherosclerotic cardiovascular disease.

Consider the risks and benefits of sitagliptin prior to initiating treatment in patients for heart failure, such as those with a prior history of heart failure and a history impairment, and observe these patients for signs and symptoms of heart failure therapy. Advise patients of the characteristic symptoms of heart failure and to imm report such symptoms. If heart failure develops, evaluate and manage according to standards of care and consider discontinuation of sitagliptin.

Assessment of Renal Function

Assessment of renal function is recommended prior to initiating sitagliptin and peri thereafter. A dosage adjustment is recommended in patients with moderate or seve impairment and in patients with ESRD requiring hemodialysis or peritoneal Caution should be used to ensure that the correct dose of sitagliptin is prescri patients with moderate (eGFR ≥30 mL/min/1.73 m2 to <45 mL/min/1.73 m2) or (eGFR <30 mL/min/1.73 m2) renal impairment.

There have been post marketing reports of worsening renal function, including acu failure, sometimes requiring dialysis. A subset of these reports involved patients wi impairment, some of whom were prescribed inappropriate doses of sitagliptin. A r baseline levels of renal impairment has been observed with supportive treatm discontinuation of potentially causative agents. Consideration can be given to ca reinitiating sitagliptin if another etiology is deemed likely to have precipitated th worsening of renal function.

Sitagliptin has not been found to be nephrotoxic in preclinical studies at clinically

4.5 Interactions with other medicinal products and other forms of Interactions
Digoxin

There was a slight increase in the area under the curve (AUC, 11%) and mean pe concentration (Cmax, 18%) of digoxin with the co-administration of 100 mg sitagl 10 days. Patients receiving digoxin should be monitored appropriately. No adjustment of digoxin or sitagliptin is recommended.

Insulin Secretagogues or Insulin

Co- administration of sitagliptin with an insulin secretagogue (e.g., sulfonylurea) or i may require lower doses of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.

4.6 Pregnancy and Lactation:
The limited available data with sitagliptin in pregnant women are not sufficient to i drug-associated risk for major birth defects and miscarriage. There are risks to the and fetus associated with poorly controlled diabetes in pregnancy. No a developmental effects were observed when sitagliptin was administered to pregn and rabbits during organogenesis at oral doses up to 30-times and 20-times, resp the 100 mg clinical dose, based on AUC.

Lactation

There is no information regarding the presence of sitagliptin in human milk, the ef the breastfed infant, or the effects on milk production. Sitagliptin is present in rat r therefore possibly present in human milk. The developmental and health ber breastfeeding should be considered along with the mother's clinical need for sitagli any potential adverse effects on the breastfed infant from sitagliptin or from the un maternal condition.

Sitagliptin is secreted in the milk of lactating rats at a milk to plasma ratio of 4:1.

4.7 Effects on ability to drive and use machine:
Data not available but being hypoglycemic drug, it can lead to hypoglycemia anc dizziness. Hence patient should be advised to not to drive machine or vehicle durir of treatment phase.

4.8 Undesirable Effects:

Innovator's published Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse r rates observed in the clinical trials of a drug cannot be directly compared to rate clinical trials of another drug and may not reflect the rates observed in practice.

In controlled clinical studies as both monotherapy and combination therapy with me pioglitazone, or rosiglitazone and metformin, the overall incidence of adverse re hypoglycemia, and discontinuation of therapy due to clinical adverse reactio sitagliptin were similar to placebo. In combination with glimepiride, with or metformin, the overall incidence of clinical adverse reactions with SITAGLIPTIN wa than with placebo, in part related to a higher incidence of hypoglycemia; the incid discontinuation due to clinical adverse reactions was similar to placebo.

Two placebo-controlled monotherapy studies, one of 18-and one of 24-week d included patients treated with SITAGLIPTIN 100 mg daily, SITAGLIPTIN 200 mg da placebo. Five placebo-controlled add-on combination therapy studies wer conducted: one with metformin; one with pioglitazone; one with metform rosiglitazone; one with glimepiride (with or without metformin); and one with insulin without metformin). In these trials, patients with inadequate glycemic control on a dose of the background therapy were randomized to add-on therapy with SITAG 100 mg daily or placebo. The adverse reactions, excluding hypoglycemia, r regardless of investigator assessment of causality in ≥5% of patients treat SITAGLIPTIN 100 mg daily and more commonly than in patients treated with place shown in Table 1 for the clinical trials of at least 18 weeks duration. Incide hypoglycemia are shown in Table 2.

Table 1:
Placebo-Controlled Clinical Studies of Sitagliptin 100 mg Monotherapy or Combination Therapy with Pioglitazone, Metformin + Rosiglitazone, or Glimepi Metformin: Adverse Reactions (Excluding Hypoglycemia) Reported in ≥ 5% of Patie More Commonly than in Patients Given Placebo, Regardless of Investigator Asse of Causality*

	Number of Patients (%)	
Monotherapy (18 or 24 weeks)	**Sitagliptin 100 mg** N= 443	**Placebo** N= 363
Nasopharyngitis	23 (5.2)	12(3.3)
Combination with Pioglitazone (24 weeks)	**Sitagliptin 100 mg + Combinat with Pioglitazone (24 weeks)** N = 175	**Placebo + Pioglitazone** N = 178
Upper respiratory tract infection	11 (6.3)	6 (3.4)
Headache	9 (5.1)	7 (3.9)
Combination with Metformin + Rosiglitazone (18 weeks)	**Sitagliptin 100 m Metformin + Rosiglitazone** N = 181	**Placebo + Metformin + Rosiglitazone N = 97**
Upper respiratory tract infection	10 (5.5)	5 (5.2)
Nasopharyngitis	11(6.1)	4 (4.1)
Combination with Glimepiride		

4.9 Overdosage:

In the event of an overdose, it is reasonable to employ supportive measures, e.g., unabsorbed material from the gastrointestinal tract, employ clinical monitoring (ir obtaining an electrocardiogram), and institute supportive therapy as dictated patient's clinical status.

Sitagliptin is modestly dialyzable. In clinical studies, approximately 13.5% of the dc removed over a 3-to 4-hour hemodialysis session. Prolonged hemodialysis r considered if clinically appropriate. It is not known if sitagliptin is dialyzable by pe dialysis.

5. Pharmacological properties

Mechanism of Action
Sitagliptin is a DPP-4 inhibitor, which is believed to exert its actions in patients with diabetes mellitus by slowing the inactivation of incretin hormones. Concentrations active intact hormones are increased by sitagliptin, thereby increasing and prolonging action of these hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal.

These hormones are rapidly inactivated by the enzyme, DPP-4. 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. 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.

5.1 Pharmacodynamic Properties:
General

In patients with type 2 diabetes mellitus, administration of sitagliptin led to inhibition of DPP-4 enzyme activity for a 24-hour period. After an oral glucose load or a meal, DPP-4 inhibition resulted in a 2-to 3-fold increase in circulating levels of active GLP-1 and GIP, decreased glucagon concentrations, and increased responsiveness of insulin secretion to glucose, resulting in higher C-peptide and insulin concentrations. The rise in insulin and the decrease in glucagon was associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal.

In studies with healthy subjects, sitagliptin did not lower blood glucose or cause hypoglycemia.

Sitagliptin and Metformin Hydrochloride Co- administration

In a two-day study in healthy subjects, sitagliptin alone increased active GLP-1 concentrations, whereas metformin alone increased active and total GLP-1 concentrations to similar extents. Co - administration of sitagliptin and metformin had an additive effect on active GLP-1 concentrations. Sitagliptin, but not metformin, increased active GIP concentrations. It is unclear how these findings relate to changes in glycemic control in patients with type 2 diabetes mellitus.

Cardiac Electrophysiology

In a randomized, placebo-controlled crossover study, 79 healthy subjects were administered a single oral dose of sitagliptin 100 mg, sitagliptin 800 mg (8 times the recommended dose), and placebo. At the recommended dose of 100 mg, there was no effect on the QTc interval obtained at the peak plasma concentration, or at any other time during the study. Following the 800 mg dose, the maximum increase in the placebo-corrected mean change in QTc from baseline was observed at 3 hours post dose and was 8.0 msec. This increase is not considered to be clinically significant. At the 800 mg

5.2 Pharmacokinetics Properties:

The pharmacokinetics of sitagliptin have been extensively characterized in subjects and patients with type 2 diabetes mellitus. In published PK study, follo single oral 100-mg dose to healthy volunteers, mean plasma AUC of sitagliptin w μM•hr, Cmax was 950 nM, and apparent terminal half-life (t1/2) was 12.4 hours. AUC of sitagliptin increased in a dose-proportional manner and increased approx 14% following 100 mg doses at steady-state compared to the first dose. The intra and inter-subject coefficients of variation for sitagliptin AUC were small (5.8% and The pharmacokinetics of sitagliptin was generally similar in healthy subjects patients with type 2 diabetes mellitus.

Absorption

After oral administration of a 100 mg dose to healthy subjects, sitagliptin was absorbed with peak plasma concentrations (median Tmax) occurring 1 to 4 postdose. The absolute bioavailability of sitagliptin is approximately 87%.

Effect of Food

Co - administration of a high-fat meal with sitagliptin had no effect on the pharmaco of sitagliptin.

Distribution

The mean volume of distribution at steady state following a single 100-mg intra dose of sitagliptin to healthy subjects is approximately 198 liters. The fraction of si reversibly bound to plasma proteins is low (38%).

Metabolism

Following a [^{14}C] sitagliptin oral dose, approximately 16% of the radioactivity was e as metabolites of sitagliptin. Six metabolites were detected at trace levels and expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin. In vitro indicated that the primary enzyme responsible for the limited metabolism of sitaglip CYP3A4, with contribution from CYP2C8.

Elimination

Approximately 79% of sitagliptin is excreted unchanged in the urine with metabolis a minor pathway of elimination. The apparent terminal t1/2 following a 100 mg oral sitagliptin was approximately 12.4 hours and renal clearance was approximately 3 min.

Following administration of an oral [^{14}C] sitagliptin dose to healthy subjects, approx 100% of the administered radioactivity was eliminated in feces (13%) or urine (87% one week of dosing.

Elimination of sitagliptin occurs primarily via renal excretion and involves active secretion. Sitagliptin is a substrate for human organic anion transporter-3 (hOAT-3 may be involved in the renal elimination of sitagliptin. The clinical relevance of hO sitagliptin transport has not been established. Sitagliptin is also a substrate glycoprotein (P-gp), which may also be involved in mediating the renal elimin

5.3 Preclinical Safety data:
Carcinogenesis, Mutagenesis, Impairment of Fertility

A two-year carcinogenicity study was conducted in male and female rats given ora of sitagliptin of 50, 150, and 500 mg/kg/day. There was an increased incide combined liver adenoma/carcinoma in males and females and of liver carcin females at 500 mg/kg. This dose results in exposures approximately 60 times the exposure at the maximum recommended daily adult human dose (MRHD) of 100 based on AUC comparisons. Liver tumors were not observed at 150 mg/kg, approx 20 times the human exposure at the MRHD. A two-year carcinogenicity stu conducted in male and female mice given oral doses of sitagliptin of 50, 125, 250, a mg/kg/day. There was no increase in the incidence of tumors in any organ up to 5 kg, approximately 70 times human exposure at the MRHD. Sitagliptin was not mu or clastogenic with or without metabolic activation in the Ames bacterial muta assay, a Chinese hamster ovary (CHO) chromosome aberration assay, an cytogenetics assay in CHO, an in vitro rat hepatocyte DNA alkaline elution assay, in vivo micronucleus assay.

In rat fertility studies with oral gavage doses of 125, 250, and 1000 mg/kg, male treated for 4 weeks prior to mating, during mating, up to scheduled terr (approximately 8 weeks total) and females were treated 2 weeks prior to mating gestation day 7. No adverse effect on fertility was observed at 125 mg/kg (approx 12 times human exposure at the MRHD of 100 mg/day based on AUC comparis higher doses, non-dose-related increased resorptions in females were ob (approximately 25 and 100 times human exposure at the MRHD based o comparison).

6. Pharmaceutical particulars

6.1 List of Excipients:

SITAPRIL 25 (Sitagliptin Tablets USP 25 mg)
Microcrystalline Cellulose
Anhydrous Dibasic Calcium Phosphate
Croscarmellose Sodium
Magnesium Stearate
Sodium Stearyl Fumarate
Instacoat Aqua II A02G10250 Peach
Purified water

SITAPRIL 50 (Sitagliptin Tablets USP 50 mg)
Microcrystalline Cellulose
Anhydrous Dibasic Calcium Phosphate
Croscarmellose Sodium
Magnesium Stearate
Sodium Stearyl Fumarate
Instacoat Aqua II A02G10249 Beige
Purified water

SITAPRIL 100 (Sitagliptin Tablets USP 100 mg)
Microcrystalline Cellulose
Anhydrous Dibasic Calcium Phosphate
Croscarmellose Sodium
Magnesium Stearate
Sodium Stearyl Fumarate
Instacoat Aqua II A02G10251 Beige
Purified water

6.2 Incompatibilities: Not Applicable

6.3 Shelf life: 24 months.

6.4 Special Precautions for storage: Store below 30°C.

6.5 Nature and contents of container:
10 tablets in Alu-Alu blister pack, 3 such blister in a printed carton along with Pack I

6.6 Special precautions for disposal: Not applicable

7. Marketing Authorization Holder:
Ajanta Pharma Limited,
Ajanta House,
Charkop, Kandivli (West),
Mumbai- 400 067,
India

8. Marketing Authorization Numbers:
TAN 21 HM 0398

9. Date of first registration /renewal of the registration:
2021-10-09

10. Date of revision of text: