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 - 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. 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 taken with or without food. **Recommendations for use in Renal Impairment** For patients with an estimated glomerular filtration rate [eGFR] greater than or equal to 45 mL/min/1.73 m^2 to less than 90 mL/min/1.73 m^2, no dosage adjustment for Sitagliptin is required. For patients with moderate renal impairment (eGFR greater than or equal to 30 mL/min/1.73 m^2 to less than 45 mL/min/1.73 m^2), the dose of Sitagliptin is 50 mg once daily. For patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2) or with end-stage renal disease (ESRD) requiring hemodialysis or peritoneal dialysis, the dose of Sitagliptin is 25 mg once daily. SITAGLIPTIN may be administered without regard to the timing of dialysis. Because there is a need for dosage adjustment based upon renal function, assessment of renal function is recommended prior to initiation of sitagliptin and periodically thereafter. There have been post marketing reports of worsening renal function in patients with renal impairment, some of whom were prescribed inappropriate doses of sitagliptin. **Pediatric Use** Safety and effectiveness of sitagliptin in pediatric patients under 18 years of age have not been established.
	4.3 Contraindications: History of a serious hypersensitivity reaction to sitagliptin, such as anaphylaxis or angioedema.
	4.4 Special warning and precautions for use: *Pancreatitis* There have been post marketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking sitagliptin. 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. It is unknown whether patients with a history of

	pancreatitis are at increased risk for the development of pancreatitis while using sitagliptin. *Heart Failure* An association between dipeptidyl peptidase-4 (DPP-4) inhibitor treatment and heart failure has been observed in cardiovascular outcomes trials for two other members of the DPP-4 inhibitor class. These trials evaluated patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease. Consider the risks and benefits of sitagliptin prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment, and observe these patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of sitagliptin. *Assessment of Renal Function* Assessment of renal function is recommended prior to initiating sitagliptin and periodically thereafter. A dosage adjustment is recommended in patients with moderate or severe renal impairment and in patients with ESRD requiring hemodialysis or peritoneal dialysis. Caution should be used to ensure that the correct dose of sitagliptin is prescribed for patients with moderate (eGFR ≥30 mL/min/1.73 m2 to <45 mL/min/1.73 m2) or severe (eGFR <30 mL/min/1.73 m2) renal impairment. There have been post marketing reports of worsening renal function, including acute renal failure, sometimes requiring dialysis. A subset of these reports involved patients with renal impairment, some of whom were prescribed inappropriate doses of sitagliptin. A return to baseline levels of renal impairment has been observed with supportive treatment and discontinuation of potentially causative agents. Consideration can be given to cautiously reinitiating sitagliptin if another etiology is deemed likely to have precipitated the acute worsening of renal function. Sitagliptin has not been found to be nephrotoxic in preclinical studies at clinically relevant doses, or in clinical trials. *Use with Medications Known to Cause Hypoglycemia* When sitagliptin was used in combination with a sulfonylurea or with insulin, medications known to cause hypoglycemia, the incidence of hypoglycemia was increased over that of placebo 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.

	Hypersensitivity Reactions There have been post marketing reports of serious hypersensitivity reactions in patients treated with Sitagliptin. 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 Sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue Sitagliptin, assess for other potential causes for the event, and institute alternative treatment for diabetes. Angioedema has also been reported with other DPP-4 inhibitors. Use caution in a patient with a history of angioedema with another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with sitagliptin. *Severe and Disabling Arthralgia* There have been post marketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate. *Bullous Pemphigoid* Post marketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving sitagliptin. If bullous pemphigoid is suspected, sitagliptin should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment. *Macrovascular Outcomes* There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with sitagliptin.
	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 peak drug concentration (Cmax, 18%) of digoxin with the co-administration of 100 mg sitagliptin for 10 days. Patients receiving digoxin should be monitored appropriately. No dosage adjustment of digoxin or sitagliptin is recommended.

	Insulin Secretagogues or Insulin Co- administration of sitagliptin with an insulin secretagogue (e.g., sulfonylurea) or insulin 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 inform a drug-associated risk for major birth defects and miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy. No adverse developmental effects were observed when sitagliptin was administered to pregnant rats and rabbits during organogenesis at oral doses up to 30-times and 20-times, respectively, the 100 mg clinical dose, based on AUC. **Lactation** There is no information regarding the presence of sitagliptin in human milk, the effects on the breastfed infant, or the effects on milk production. Sitagliptin is present in rat milk and therefore possibly present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for sitagliptin and any potential adverse effects on the breastfed infant from sitagliptin or from the underlying 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 and further dizziness. Hence patient should be advised to not to drive machine or vehicle during initial of treatment phase.
	4.8 Undesirable Effects: **Innovator's published Clinical Trials Experience** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the 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 metformin, pioglitazone, or rosiglitazone and metformin, the overall incidence of adverse reactions, hypoglycemia, and discontinuation of therapy due to clinical adverse reactions with sitagliptin were similar to placebo. In combination with glimepiride, with or without metformin, the overall incidence of clinical adverse reactions with SITAGLIPTIN was higher than with placebo, in part related to a higher incidence of hypoglycemia; the incidence of discontinuation due to clinical adverse reactions was similar to placebo.

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

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

	Number of Patients (%)	
Monotherapy (18 or 24 weeks)	**Sitagliptin 100 mg**	**Placebo**
	N= 443	N= 363
Nasopharyngitis	23 (5.2)	12(3.3)
Combination with Pioglitazone (24 weeks)	**Sitagliptin 100 mg + Combination with Pioglitazone (24 weeks)**	**Placebo + Pioglitazone**
	N = 175	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 mg + Metformin + Rosiglitazone**	**Placebo + Metformin + Rosiglitazone**
	N = 181	**N = 97**
Upper respiratory tract infection	10 (5.5)	5 (5.2)
Nasopharyngitis	11(6.1)	4 (4.1)
Combination with Glimepiride (+/- Metformin) (24 weeks)	**Sitagliptin 100 mg + Glimepiride (+/- Metformin)**	**Placebo + Glimepiride (+/- Metformin)**

	N = 222	N = 219
Nasopharyngitis	14 (6.3)	10 (4.6)
Headache	13 (5.9)	5 (2.3)

* Intent-to-treat population

In the 24-week study of patients receiving SITAGLIPTIN as add-on combination therapy with metformin, there were no adverse reactions reported regardless of investigator assessment of causality in ≥5% of patients and more commonly than in patients given placebo.

In the 24-week study of patients receiving SITAGLIPTIN as add-on therapy to insulin (with or without metformin), there were no adverse reactions reported regardless of investigator assessment of causality in ≥5% of patients and more commonly than in patients given placebo, except for hypoglycemia.(Table 2)

Table 2:
Incidence and Rate of Hypoglycemia* in Placebo-Controlled Clinical Studies when JANUVIA was used as Add-On Therapy to Glimepiride (with or without Metformin) or Insulin (with or without Metformin), Regardless of Investigator Assessment of Causality

Add-On to Glimepiride (+/- Metformin) (24 weeks)	**Sitagliptin 100 mg + Glimepiride (+/- Metformin)**	**Placebo + Glimepiride (+/- Metformin)**
	N= 222	N = 219
Overall (%)	27 (12.2)	4 (1.8)
Rate (episodes/patient-year)†	0.59	0.24
Severe (%) ‡	0 (0.0)	0 (0.0)
Add-On to Insulin (+/- Metformin) (24 weeks)	**Sitagliptin 100 mg + Insulin (+/- Metformin)**	**Placebo + Insulin (+/- Metformin)**
	N =332	N = 319
Overall (%)	50 (15.5)	25 (7.8)
Rate (episodes/patient-year)†	1.06	0.51
Severe (%) ‡	2 (0.6)	1(0.3)

* Adverse reactions of hypoglycemia were based on all reports of symptomatic hypoglycemia; a concurrent glucose measurement was not required; intent-to-treat population.
† Based on total number of events (i.e., a single patient may have had multiple events).
‡ Severe events of hypoglycemia were defined as those events requiring medical assistance or exhibiting depressed level/loss of consciousness or seizure.

	In the study of SITAGLIPTIN as add-on combination therapy with metformin and rosiglitazone, through Week 54 the adverse reactions reported regardless of investigator assessment of causality in ≥5% of patients treated with SITAGLIPTIN and more commonly than in patients treated with placebo were: upper respiratory tract infection (SITAGLIPTIN, 15.5%; placebo, 6.2%), nasopharyngitis (11.0%, 9.3%), peripheral edema (8.3%, 5.2%), and headache (5.5%, 4.1%). In a pooled analysis of the two monotherapy studies, the add-on to metformin study, and the add-on to pioglitazone study, the incidence of selected gastrointestinal adverse reactions in patients treated with SITAGLIPTIN was as follows: abdominal pain (SITAGLIPTIN 100 mg, 2.3%; placebo, 2.1%), nausea (1.4%, 0.6%), and diarrhea (3.0%, 2.3%). No clinically meaningful changes in vital signs or in ECG (including in QTc interval) were observed in patients treated with SITAGLIPTIN. In a pooled analysis of 19 double-blind clinical trials that included data from 10,246 patients randomized to receive sitagliptin 100 mg/day (N=5429) or corresponding (active or placebo) control (N=4817), the incidence of acute pancreatitis was 0.1 per 100 patient-years in each group (4 patients with an event in 4708 patient-years for sitagliptin and 4 patients with an event in 3942 patient-years for control). **Hypoglycemia** In the above studies (N=9), adverse reactions of hypoglycemia were based on all reports of symptomatic hypoglycemia. A concurrent blood glucose measurement was not required although most (74%) reports of hypoglycemia were accompanied by a blood glucose measurement ≤70 mg/dL. When SITAGLIPTIN was co - administered with a sulfonylurea or with insulin, the percentage of patients with at least one adverse reaction of hypoglycemia was higher than in the corresponding placebo group. **Laboratory Tests** Across clinical studies, the incidence of laboratory adverse reactions was similar in patients treated with SITAGLIPTIN 100 mg compared to patients treated with placebo. A small increase in white blood cell count (WBC) was observed due to an increase in neutrophils. This increase in WBC (of approximately 200 cells/microL vs placebo, in four pooled placebo-controlled clinical studies, with a mean baseline WBC count of approximately 6600 cells/microL) is not considered to be clinically relevant. In a 12-week study of 91 patients with chronic renal insufficiency, 37 patients with moderate renal insufficiency were randomized to SITAGLIPTIN 50 mg daily, while 14 patients with the same magnitude of renal impairment were randomized to placebo. Mean (SE) increases in serum creatinine were observed in patients treated with SITAGLIPTIN [0.12 mg/dL (0.04)] and in patients treated with placebo [0.07 mg/dL (0.07)]. The clinical significance of this added increase in serum creatinine relative to placebo is not known.

	Post marketing Experience Additional adverse reactions have been identified during post approval use of SITAGLIPTIN as monotherapy and/or in combination with other anti-hyperglycemic agents. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions including Stevens-Johnson syndrome; hepatic enzyme elevations; acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis; worsening renal function, including acute renal failure (sometimes requiring dialysis); severe and disabling arthralgia; bullous pemphigoid; constipation; vomiting; headache; myalgia; pain in extremity; back pain; pruritus; mouth ulceration; stomatitis; rhabdomyolysis.
	4.9 Overdosage: In the event of an overdose, it is reasonable to employ 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. In clinical studies, approximately 13.5% of the dose was removed over a 3-to 4-hour hemodialysis session. Prolonged hemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialyzable by peritoneal dialysis.
5.	**Pharmacological properties**
	Mechanism of Action Sitagliptin is a DPP-4 inhibitor, which is believed to exert its actions in patients with type 2 diabetes mellitus by slowing the inactivation of incretin hormones. Concentrations of the active intact hormones are increased by sitagliptin, thereby increasing and prolonging the 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, this 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 release to glucose, resulting in higher C-peptide and insulin concentrations. The rise in insulin with 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 dose, peak sitagliptin plasma concentrations were approximately 11 times higher than the peak concentrations following a 100-mg dose. In patients with type 2 diabetes mellitus administered sitagliptin 100 mg (N=81) or sitagliptin 200 mg (N=63) daily, there were no meaningful changes in QTc interval based on ECG data obtained at the time of expected peak plasma concentration.
	5.2 Pharmacokinetics Properties: The pharmacokinetics of sitagliptin have been extensively characterized in healthy subjects

	and patients with type 2 diabetes mellitus. In published PK study, following a single oral 100-mg dose to healthy volunteers, mean plasma AUC of sitagliptin was 8.52 µM•hr, Cmax was 950 nM, and apparent terminal half-life (t1/2) was 12.4 hours. Plasma AUC of sitagliptin increased in a dose-proportional manner and increased approximately 14% following 100 mg doses at steady-state compared to the first dose. The intra-subject and inter-subject coefficients of variation for sitagliptin AUC were small (5.8% and 15.1%). The pharmacokinetics of sitagliptin was generally similar in healthy subjects and in patients with type 2 diabetes mellitus. *Absorption* After oral administration of a 100 mg dose to healthy subjects, sitagliptin was rapidly absorbed with peak plasma concentrations (median Tmax) occurring 1 to 4 hours 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 pharmacokinetics of sitagliptin. *Distribution* The mean volume of distribution at steady state following a single 100-mg intravenous dose of sitagliptin to healthy subjects is approximately 198 liters. The fraction of sitagliptin reversibly bound to plasma proteins is low (38%). *Metabolism* Following a [^{14}C] sitagliptin oral dose, approximately 16% of the radioactivity was excreted as metabolites of sitagliptin. Six metabolites were detected at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin. In vitro studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin was CYP3A4, with contribution from CYP2C8. *Elimination* Approximately 79% of sitagliptin is excreted unchanged in the urine with metabolism being a minor pathway of elimination. The apparent terminal t1/2 following a 100 mg oral dose of sitagliptin was approximately 12.4 hours and renal clearance was approximately 350 mL/min. Following administration of an oral [^{14}C] sitagliptin dose to healthy subjects, approximately 100% of the administered radioactivity was eliminated in feces (13%) or

	urine (87%) within one week of dosing. Elimination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion. Sitagliptin is a substrate for human organic anion transporter-3 (hOAT-3), which may be involved in the renal elimination of sitagliptin. The clinical relevance of hOAT-3 in sitagliptin transport has not been established. Sitagliptin is also a substrate of P-glycoprotein (P-gp), which may also be involved in mediating the renal elimination of sitagliptin. However, cyclosporine, a P-gp inhibitor, did not reduce the renal clearance of sitagliptin.
	5.3 Preclinical Safety data: *Carcinogenesis, Mutagenesis, Impairment of Fertility* A two-year carcinogenicity study was conducted in male and female rats given oral doses of sitagliptin of 50, 150, and 500 mg/kg/day. There was an increased incidence of combined liver adenoma/carcinoma in males and females and of liver carcinoma in females at 500 mg/kg. This dose results in exposures approximately 60 times the human exposure at the maximum recommended daily adult human dose (MRHD) of 100 mg/day based on AUC comparisons. Liver tumors were not observed at 150 mg/kg, approximately 20 times the human exposure at the MRHD. A two-year carcinogenicity study was conducted in male and female mice given oral doses of sitagliptin of 50, 125, 250, and 500 mg/kg/day. There was no increase in the incidence of tumors in any organ up to 500 mg/kg, approximately 70 times human exposure at the MRHD. Sitagliptin was not mutagenic or clastogenic with or without metabolic activation in the Ames bacterial mutagenicity assay, a Chinese hamster ovary (CHO) chromosome aberration assay, an in vitro cytogenetics assay in CHO, an in vitro rat hepatocyte DNA alkaline elution assay, and an in vivo micronucleus assay. In rat fertility studies with oral gavage doses of 125, 250, and 1000 mg/kg, males were treated for 4 weeks prior to mating, during mating, up to scheduled termination (approximately 8 weeks total) and females were treated 2 weeks prior to mating through gestation day 7. No adverse effect on fertility was observed at 125 mg/kg (approximately 12 times human exposure at the MRHD of 100 mg/day based on AUC comparisons). At higher doses, non-dose-related increased resorptions in females were observed (approximately 25 and 100 times human exposure at the MRHD based on AUC 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: 2 Years.
	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 Insert.
	6.6 Special precautions for disposal: Not applicable
7.	**Marketing Authorization Holder:** Ajanta Pharma Limited Ajanta House, Charkop, Kandivli (West), Mumbai- 400 067, India **Manufacturing Site Address:** Ajanta Pharma Limited B-4-5-6, MIDC Industrial Area Paithan, Aurangabad, 431148 Dist: Aurangabad

	Maharashtra, India.
8.	**Marketing Authorization Numbers:** Not applicable
9.	**Date of first registration /renewal of the registration:** Not Applicable
10.	**Date of revision of text:** October 30, 2020