1. **Name of the Medicinal Product**
   Ziglip – 50 (Sitagliptin Tablets USP 50 mg)

2. **Qualitative & Quantitative Composition**
   Each film coated tablet contains:
   Sitagliptin Phosphate Monohydrate USP
   Equivalent to Sitagliptin…….50 mg
   Excipients: q.s
   Colour: Titanium dioxide

Qualitative and Quantitative Composition **Batch Size: 25000 Tablets**

Sr. No.	Ingredient	Specification	Overages	Input Qty per dose in mg	Actual Qty. Batch/Kg	Rationale
1.	*Sitagliptin Phosphate Monohydrate Equiv. to Sitagliptin …. 50.00 mg	USP	--	64.25	1.606	Active
Dry Mixing						
2.	**Microcrystalline Cellulose PH 101	BP	--	104.75	2.619	Diluent
3.	Anhydrous Calcium hydrogen Phosphate	BP	--	11.00	0.275	Diluent
Binder						
4.	Povidone K-30	BP	--	6.00	0.150	Binder
5.	Iso propyl alcohol	BP	--	0.1275 mL	3.188 L	Solvent
Pre-Lubrication						
6.	Croscarmellose sodium	USP	--	6.00	0.150	Disintegrant
7.	Sodium Stearyl Fumarate	BP	--	4.00	0.100	Glidant
Lubrication						
8.	Magnesium Stearate	BP	--	4.00	0.100	Lubricant
Total Core tablet weight				200.00	5.00	
Coating						
9.	Instamoistshield AQ II white A22R01100	IH	--	5.00	0.125	Coating material
10	Purified Water	BP	--	0.029mL	0.725	Solvent
Total Coated tablet weight				205.00	5.125	--

2% extra material for machine settings.
* On Anhydrous Basis
** Adjust quantity to be dispensed based on Sitagliptin Phosphate Monohydrate dispensing quantity.

3. **Pharmaceutical form**

Pharmaceutical Form – Film Coated Tablet

Product Description - White to off white coloured, round shaped tablets with breakline on one side and plain on other side.

4. **Clinical Particulars**

4.1. Therapeutic Indications

For adult patients with type 2 diabetes mellitus, Sitagliptin is indicated to improve glycaemic control: as monotherapy

- In patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance
  as dual oral therapy in combination with
- A sulphonylurea when diet and exercise plus maximal tolerated dose of a sulphonylurea alone do not provide adequate glycaemic control
- A peroxisome proliferator-activated receptor gamma (PPARγ) agonist (i.e. a thiazolidinedione) when use of a PPARγ agonist is appropriate and when diet and exercise plus the PPARγ agonist alone do not provide adequate glycaemic control.
- Sitagliptin is also indicated as add-on to insulin when diet and exercise plus stable dose of insulin do not provide adequate glycaemic control.

4.2. Posology & Method of administration

Posology

The dose is 100 mg sitagliptin once daily. When used in combination with a PPARγ agonist, the dose of PPARγ agonist should be maintained, and sitagliptin administered concomitantly.

When sitagliptin is used in combination with a sulphonylurea or with insulin, a lower dose of the sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia.

If a dose of 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 impairment

When considering the use of sitagliptin in combination with another anti-diabetic medicinal 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 < 90 ml/min), no dose adjustment is required.

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

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

For patients with severe renal impairment (GFR ≥ 15 to < 30 ml/min) or with end stage renal disease (ESRD) (GFR < 15 ml/min), including those requiring haemodialysis or peritoneal dialysis, the dose of sitagliptin is 25 mg once daily. Treatment may be administered without regard to the timing of dialysis.

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

Hepatic impairment
No dose adjustment is necessary for patients with mild to moderate hepatic impairment. Sitagliptin has not been studied in patients with severe hepatic impairment and care should be exercised.
However, because sitagliptin is primarily renally eliminated, severe hepatic impairment is not expected to affect the pharmacokinetics of sitagliptin.

Elderly
No dose adjustment is necessary based on age.

Paediatric population
The safety and efficacy of sitagliptin in children and adolescents under 18 years of age have not yet been established. No data are available.

Method of administration
Sitagliptin can be taken with or without food.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients listed.

4.4 Special warnings and precautions for use
General
Sitagliptin should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

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

Hypoglycaemia when used in combination with other anti-hyperglycaemic medicinal products
In clinical trials of sitagliptin as monotherapy and as part of combination therapy with medicinal products not known to cause hypoglycaemia (i.e. a PPARγ agonist), rates of hypoglycaemia reported with sitagliptin were similar to rates in patients taking placebo.
Hypoglycaemia has been observed when sitagliptin was used in combination with insulin or a sulphonylurea. Therefore, to reduce the risk of hypoglycaemia, a lower dose of sulphonylurea or insulin may be considered.

Renal impairment

Sitagliptin is renally excreted. To achieve plasma concentrations of sitagliptin similar to those in patients with normal renal function, lower dosages are recommended in patients with GFR < 45 ml/min, as well as in ESRD patients requiring haemodialysis or peritoneal dialysis.

When considering the use of sitagliptin in combination with another antidiabetic medicinal product, its conditions for use in patients with renal impairment should be checked.

Hypersensitivity reactions

Post-marketing reports of serious hypersensitivity reactions in patients treated with sitagliptin have been reported. 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 some reports occurring.

after the first dose. If a hypersensitivity reaction is suspected, sitagliptin should be discontinued. Other potential causes for the event should be assessed, and alternative treatment for diabetes initiated.

Bullous pemphigoid

There have been post-marketing reports of bullous pemphigoid in patients taking DPP4 inhibitors including sitagliptin. If bullous pemphigoid is suspected, sitagliptin should be discontinued.

Excipients

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

This medicine contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other interactions

Effects of other medicinal products on sitagliptin

Clinical data described below suggest that the risk for clinically meaningful interactions by co-administered medicinal products is low.

In vitro studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin is CYP3A4, with contribution from CYP2C8. In patients with normal renal function, metabolism, including via CYP3A4, plays only a small role in the clearance of sitagliptin. Metabolism may play a more significant role in the elimination of sitagliptin in the setting of severe renal impairment or end-stage renal disease (ESRD). For this reason, it is possible that potent CYP3A4 inhibitors (i.e. ketoconazole, itraconazole, ritonavir, clarithromycin) could alter the pharmacokinetics of sitagliptin inpatients with severe renal impairment or ESRD. The effect of potent CYP3A4 inhibitors in the setting of renal impairment has not been assessed in a clinical study.

In vitro transport studies showed that sitagliptin is a substrate for pglycoprotein and organic anion transporter-3 (OAT3). OAT3 mediated transport of sitagliptin was inhibited in vitro by probenecid, although the risk of clinically meaningful interactions is considered to be low.

Concomitant administration of OAT3 inhibitors has not been evaluated in vivo.
Ciclosporin: A study was conducted to assess the effect of ciclosporin, a potent inhibitor of p- glycoprotein, on the pharmacokinetics of sitagliptin. Coadministration of a single 100 mg oral dose of sitagliptin and a single 600 mg oral dose of ciclosporin increased the AUC and Cmax of sitagliptin by approximately 29 % and 68 %, respectively. These changes in sitagliptin pharmacokinetics were not considered to be clinically meaningful. The renal clearance of sitagliptin was not meaningfully altered. Therefore, meaningful interactions would not be expected with other p-glycoprotein inhibitors.

Effects of sitagliptin on other medicinal products

Digoxin: Sitagliptin had a small effect on plasma digoxin concentrations. Following administration of 0.25 mg digoxin concomitantly with 100 mg of sitagliptin daily for 10 days, the plasma AUC of digoxin was increased on average by 11 %, and the plasma Cmax on average by 18 %. No dose adjustment of digoxin is recommended. However, patients at risk of digoxin toxicity should be monitored for this when sitagliptin and digoxin are administered concomitantly. In vitro data suggest that sitagliptin does not inhibit nor induce CYP450 isoenzymes. In clinical studies, sitagliptin did not meaningfully alter the pharmacokinetics of glyburide, simvastatin, rosiglitazone, warfarin, or oral contraceptives, providing in vivo evidence of a low propensity for causing interactions with substrates of CYP3A4, CYP2C8, CYP2C9, and organic cationic transporter (OCT). Sitagliptin may be a mild inhibitor of p- glycoprotein in vivo.

4.6 Pregnancy and Lactation

Pregnancy

There are no adequate data from the use of sitagliptin in pregnant women. Studies in animals have shown reproductive toxicity at high doses (see section 5.3). The potential risk for humans is unknown. Due to lack of human data, sitagliptin should not be used during pregnancy.

Lactation

It is unknown whether sitagliptin is excreted in human breast milk. Animal studies have shown excretion of sitagliptin in breast milk. Sitagliptin should not be used during breast- feeding.

Fertility

Animal data do not suggest an effect of treatment with sitagliptin on male and female fertility. Human data are lacking.

4.7 Effects on ability to drive and use machines

Sitagliptin has no or negligible influence on the ability to drive and use machines. However, when driving or using machines, it should be taken into account that dizziness and somnolence have been reported.
In addition, patients should be alerted to the risk of hypoglycaemia when sitagliptin is used in combination with a sulphonylurea or with insulin.

4.8 Undesirable Effects

Summary of the safety profile

Serious adverse reactions including pancreatitis and hypersensitivity reactions have been reported. Hypoglycaemia has been reported in combination with sulphonylurea (4.7 %-13.8 %) and insulin (9.6 %).

Tabulated list of adverse reactions

Adverse reactions are listed below (Table 1) by system organ class and frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000) and not known (cannot be estimated from the available data).

Table 1. The frequency of adverse reactions identified from placebo-controlled clinical studies of sitagliptin monotherapy and post-marketing experience

Adverse reaction	Frequency of adverse reaction
Blood and Lymphatic system disorders	
Thrombocytopenia	Rare
Immune system disorders	
Hypersensitive reaction including anaphylactic responses	Frequency not common
Metabolism and nutritional disorders	
Hypoglycemia	Common
Nervous system disorders	
Headache	Common
Dizziness	Uncommon

Adverse Reaction	**Frequency of adverse reaction**
Respiratory thoracic and mediastinal disorders	
Interstitial lung disease	Frequency not known
Gastrointestinal disorders	

Constipation	Uncommon
Vomiting	Frequency not known
Acute pancreatitis'	Frequency not known
Fatal and non-fatal haemorrhagic and necrotizing pancreatitis	Frequency not known
Skin and subcutaneous tissue disorders	
Pruritus	Uncommon
Angioedema	Frequency not known
Rash	Frequency not known
Urticaria	Frequency not known
Cutaneous vasculitis	Frequency not known
Exfoliative skin conditions including stevens Johnson syndrome	Frequency not known
Bullous pemphigoid	Frequency not known
Musculoskeletal and connective tissue Disorders	
Arthralgia	Frequency not known
Myalgia	Frequency not known
Back pain	Frequency not known
Arthropathy	Frequency not known
Renal and Urinary disorders	Frequency not known
Impaired renal function	Frequency not known

*Adverse reactions were identified through postmarketing surveillance.

‡ See TECOS Cardiovascular Safety Study below.

Description of selected adverse reactions

In addition to the drug-related adverse experiences described above, adverse experiences reported regardless of causal relationship to medication and occurring in at least 5 % and more commonly in patients treated with sitagliptin included upper respiratory tract infection and nasopharyngitis.

Additional adverse experiences reported regardless of causal relationship to medication that occurred more frequently in patients treated with sitagliptin (not reaching the 5 % level, but occurring with an incidence of > 0.5 % higher with sitagliptin than that in the control group) included osteoarthritis and pain in extremity.

Some adverse reactions were observed more frequently in studies of combination use of sitagliptin with other anti-diabetic medicinal products than in studies of sitagliptin monotherapy. These included influenza (common with insulin flatulence (common with pioglitazone), peripheral oedema (common with pioglitazone), somnolence and diarrhoea, and dry mouth (uncommon with insulin).

TECOS Cardiovascular Safety Study

The Trial Evaluating Cardiovascular Outcomes with sitagliptin (TECOS) included 7,332 patients treated with sitagliptin, 100 mg daily (or 50 mg daily if the baseline eGFR was ≥ 30 and < 50 ml/min/1.73 m2), and 7,339 patients treated with placebo in the intention-to-treat population. Both treatments were added to usual care targeting regional standards for HbA1c and CV risk factors. The overall incidence of serious adverse events in patients receiving sitagliptin was similar to that in patients receiving placebo.

In the intention-to-treat population, among patients who were using insulin and/or a sulfonylurea at baseline, the incidence of severe hypoglycaemia was 2.7 % in sitagliptin- treated patients and 2.5 % in placebo-treated patients; among patients who were not using insulin and/or a sulfonylurea at baseline, the incidence of severe hypoglycaemia was 1.0 % in sitagliptin-treated patients and 0.7 % in placebo-treated patients. The incidence of adjudication-confirmed pancreatitis events was 0.3 % in sitagliptin-treated patients and 0.2 % in placebo-treated patients.

4.9 Overdose

During controlled clinical trials in healthy subjects, single doses of up to 800 mg sitagliptin were administered. Minimal increases in QTc, not considered to be clinically relevant, were observed in one study at a dose of 800 mg sitagliptin. There is no experience with doses above 800 mg in clinical studies. In Phase I multiple-dose studies, there were no dose- related clinical adverse reactions observed with sitagliptin with doses of up to 600 mg per day for periods of up to 10 days and 400 mg per day for periods of up to 28 days.

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 if required.

Sitagliptin is modestly dialysable. In clinical studies, approximately 13.5 % of the dose was removed over a 3- to 4-hour haemodialysis session. Prolonged haemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialysable by peritoneal dialysis.

5 Pharmacological Properties

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Drugs used in diabetes, Dipeptidyl peptidase 4 (DPP-4) inhibitors.

ATC code: A10BH01

Mechanism of action:

Sitagliptin is a member of a class of oral anti-hyperglycaemic agents called dipeptidyl peptidase 4 (DPP-4) inhibitors. The improvement in glycaemic control observed with this medicinal product may be mediated by enhancing the levels of active incretin hormones. Incretin hormones, including glucagonlike 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. 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 signalling pathways

involving cyclic AMP. Treatment with GLP-1 or with DPP-4 inhibitors in animal models of type 2 diabetes has been demonstrated to improve beta cell responsiveness to glucose and stimulate insulin biosynthesis and release. With higher insulin levels, tissue glucose uptake is enhanced. In addition, GLP-1 lowers glucagon secretion from pancreatic alpha cells. Decreased glucagon concentrations, along with higher insulin levels, lead to reduced hepatic glucose production, resulting in a decrease in blood glucose levels. The effects of GLP-1 and GIP are glucose-dependent such that when blood glucose concentrations are low, stimulation of insulin release and suppression of glucagon secretion by GLP-1 are not observed. For both GLP-1 and GIP, stimulation of insulin release is enhanced as glucose rises above normal concentrations. Further, GLP-1 does not impair the normal glucagon response to hypoglycaemia. The activity of GLP-1 and GIP is limited by the DPP-4 enzyme, which rapidly hydrolyses the incretin hormones to produce inactive products. Sitagliptin prevents the hydrolysis of incretin hormones by DPP-4, thereby increasing plasma concentrations of the active forms of GLP-1 and GIP. By enhancing active incretin levels, sitagliptin increases insulin release and decreases glucagon levels in a glucose dependent manner. In patients with type 2 diabetes with hyperglycaemia, these changes in insulin and glucagon levels lead to lower haemoglobin A1c (HbA1c) and lower fasting and postprandial glucose concentrations. The glucose-dependent mechanism of sitagliptin is distinct from the mechanism of sulphonylureas, which increase insulin secretion even when glucose levels are low and can lead to hypoglycaemia in patients with type 2 diabetes and in normal subjects.
Sitagliptin is a potent and highly selective inhibitor of the enzyme DPP-4 and does not inhibit the closely related enzymes DPP-8 or DPP-9 at therapeutic concentrations.
In a two-day study in healthy subjects, sitagliptin alone increased active GLP1 concentrations, whereas metformin alone increased active and total GLP-1 concentrations to similar extents.

Clinical efficacy and safety

Overall, sitagliptin improved glycaemic control when used as monotherapy or in combination treatment.
Two studies were conducted to evaluate the efficacy and safety of sitagliptin monotherapy. Treatment with sitagliptin at 100 mg once daily as monotherapy provided significant improvements in HbA1c, fasting plasma glucose (FPG), and 2hour post-prandial glucose (2- hour PPG), compared to placebo in two studies, one of 18- and one of 24-weeks duration. Improvement of surrogate markers of beta cell function, including HOMA-β (Homeostasis Model Assessment-β), proinsulin to insulin ratio, and measures of beta cell responsiveness from the frequently-sampled meal tolerance test were observed. The observed incidence of hypoglycaemia in patients treated with sitagliptin was similar to placebo. Body weight did not increase from baseline with sitagliptin therapy in either study, compared to a small reduction in patients given placebo.
Sitagliptin 100 mg once daily provided significant improvements in glycaemic parameters compared with placebo in a 24-week studies of sitagliptin as add-on therapy in combination with pioglitazone. Change from baseline in body weight was similar for patients treated with sitagliptin relative to placebo. In these studies there was a similar incidence of hypoglycaemia reported for patients treated with sitagliptin or placebo.
A 24-week placebo-controlled study was designed to evaluate the efficacy and safety of sitagliptin (100 mg once daily) added to glimepiride alone. The addition of sitagliptin leads to glimepiride

alone significant improvements in glycaemic parameters. Patients treated with sitagliptin had a modest increase in body weight compared to those given placebo.

A 24-week placebo-controlled study was designed to evaluate the efficacy and safety of sitagliptin (100 mg once daily) added to insulin (at a stable dose for at least 10 weeks) with or without metformin (at least 1,500 mg). In patients taking pre-mixed insulin, the mean daily dose was 70.9 U/day. In patients taking non-pre-mixed (intermediate/longacting) insulin, the mean daily dose was 44.3 U/day.

The addition of sitagliptin to insulin provided significant improvements in glycaemic parameters. There was no meaningful change from baseline in body weight in either group.

Table 2. HbA1c results in placebo-controlled monotherapy and combination therapy studies *

Study	Mean baseline HbA1c (%)	Mean change from baseline HbA1c (%)†	Placebo-corrected mean change in HbA1c (%) † (95 %CI)
Monotherapy Studies			
Sitagliptin 100 mg once daily§ (N= 193)	8.0	-0.5	-0.6‡ (-0.8, -0.4)
Sitagliptin 100 mg once daily% (N= 229)	8.0	-0.6	-0.8‡ (-1.0, -0.6)
Combination Therapy Studies			
Sitagliptin 100 mg once daily added to ongoing metformin therapy% (N=453)	8.0	-0.7	-0.7‡ (-0.8, -0.5)
Sitagliptin 100 mg once daily added to ongoing pioglitazone therapy% (N=163)	8.1	-0.9	-0.7‡ (-0.9, -0.5)
Sitagliptin 100 mg once daily added to ongoing glimepiride therapy% (N=102)	8.4	-0.3	-0.6‡ (-0.8, -0.3)
Sitagliptin 100 mg once daily added to ongoing glimepiride + metformin therapy% (N=115)	8.3	-0.6	-0.9‡ (-1.1, -0.7)
Sitagliptin 100 mg once daily added to ongoing pioglitazone + metformin therapy# (N=152)	8.8	-1.2	-0.7‡ (-1.0, -0.5)
Initial therapy (twice daily)%: Sitagliptin 50 mg + metformin 500 mg (N=183)	8.8	-1.4	-1.6‡ (-1.8, -1.3)
Initial therapy (twice daily)%: Sitagliptin 50 mg + metformin 1,000 mg (N=178)	8.8	-1.9	-2.1‡ (-2.3, -1.8)
Sitagliptin 100 mg once daily added to ongoing insulin (+/- metformin) therapy% (N=305)	8.7	-0.6¶	-0.6‡,¶ (-0.7, -0.4)

* All patients treated population (an intention-to-treat analysis).

† Least squares means adjusted for prior antihyperglycaemic therapy status and baseline value.

‡ p< 0.001 compared to placebo or placebo + combination treatment.
§ HbA1c (%) at week 18. % HbA1c (%) at week 24. # HbA1c (%) at week 26.

¶ A 24-week active (metformin)-controlled study was designed to evaluate the efficacy and safety of sitagliptin 100 mg once daily (n=528) compared to metformin (n=522) in patients with inadequate glycaemic control on diet and exercise and who were not on anti- hyperglycaemic therapy (off therapy for at least 4 months). The mean dose of metformin was approximately 1,900 mg per day. The reduction in HbA1c from mean baseline values of 7.2 % was -0.43 % for sitagliptin and -0.57 % for metformin (Per Protocol Analysis). The overall incidence of gastrointestinal adverse reactions considered as drug-related in patients treated with sitagliptin was 2.7 % compared with 12.6 % in patients treated with metformin. The incidence of hypoglycaemia was not significantly different between the treatment groups (sitagliptin, 1.3 %; metformin, 1.9 %). Body weight decreased from baseline in both groups (sitagliptin, -0.6 kg; metformin -1.9 kg).
In a study comparing the efficacy and safety of the addition of glipizide (a sulphonylurea) in patients with inadequate glycaemic control on metformin monotherapy, glipizide could reduce HbA1c. The mean glipizide dose used in the comparator group was 10 mg per day with approximately 40 % of patients requiring a glipizide dose of ≤ 5 mg/day throughout the study.
A 24-week placebo-controlled study involving 660 patients was designed to evaluate the insulin-sparing efficacy and safety of sitagliptin (100 mg once daily) added to insulin glargine during intensification of insulin therapy. Baseline HbA1c was 8.74 % and baseline insulin dose was 37 IU/day. Patients were instructed to titrate their insulin glargine dose based on fingerstick fasting glucose values. At Week 24, the increase in daily insulin dose was 19 IU/day in patients treated with sitagliptin and 24 IU/day in patients treated with placebo. The reduction in HbA1c in patients treated with sitagliptin and insulin was -1.31 % compared to -0.87 % in patients treated with placebo and insulin, a difference of -0.45 % [95 % CI: 0.60, -0.29]. The incidence of hypoglycaemia was 25.2 % in patients treated with sitagliptin and insulin and 36.8 % in patients treated with placebo and insulin. The difference was mainly due to a higher percentage of patients in the placebo group experiencing 3 or more episodes of hypoglycaemia (9.4 vs. 19.1 %). There was no difference in the incidence of severe hypoglycaemia.
A study comparing sitagliptin at 25 or 50 mg once daily to glipizide at 2.5 to 20 mg/day was conducted in patients with moderate to severe renal impairment. This study involved 423 patients with chronic renal impairment (estimated glomerular filtration rate < 50 ml/min). After 54 weeks, the mean reduction from baseline in HbA1c was 0.76 % with sitagliptin and - 0.64 % with glipizide (Per-Protocol Analysis). In this study, the efficacy and safety profile of sitagliptin at 25 or 50 mg once daily was generally similar to that observed in other monotherapy studies in patients with normal renal function. The incidence of hypoglycaemia in the sitagliptin group (6.2 %) was significantly lower than that in the glipizide group (17.0 %). There was also a significant difference between groups with respect to change from baseline body weight (sitagliptin -0.6 kg; glipizide +1.2 kg).
Another study comparing sitagliptin at 25 mg once daily to glipizide at 2.5 to 20 mg/day was conducted in 129 patients with ESRD who were on dialysis. After 54 weeks, the mean reduction from baseline in HbA1c was -0.72 % with sitagliptin and 0.87 % with glipizide. In this study, the efficacy and safety profile of sitagliptin at 25 mg once daily was generally similar to that observed

in other monotherapy studies in patients with normal renal function. The incidence of hypoglycaemia was not significantly different between the treatment groups (sitagliptin, 6.3 %; glipizide, 10.8 %).
In another study involving 91 patients with type 2 diabetes and chronic renal impairment (creatinine clearance < 50 ml/min), the safety and tolerability of treatment with sitagliptin at 25 or 50 mg once daily were generally similar to placebo. In addition, after 12 weeks, the mean reductions in HbA1c (sitagliptin -0.59 %; placebo -0.18 %) and FPG (sitagliptin -25.5 mg/dl; placebo -3.0 mg/dl) were generally similar to those observed in other monotherapy studies in patients with normal renal function.
The TECOS was a randomised study in 14,671 patients in the intention-totreat population with an HbA1c of ≥ 6.5 to 8.0 % with established CV disease who received sitagliptin (7,332) 100 mg daily (or 50 mg daily if the baseline eGFR was ≥ 30 and < 50 ml/min/1.73 m2) or placebo (7,339) added to usual care targeting regional standards for HbA1c and CV risk factors. Patients with an eGFR < 30 ml/min/1.73 m2 were not to be enrolled in the study. The study population included 2,004 patients ≥ 75 years of age and 3,324 patients with renal impairment (eGFR < 60 ml/min/1.73 m2).
Over the course of the study, the overall estimated mean (SD) difference in HbA1c between the sitagliptin and placebo groups was 0.29 % (0.01), 95 % CI (-0.32, -0.27); p < 0.001.
The primary cardiovascular endpoint was a composite of the first occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalisation for unstable angina. Secondary cardiovascular endpoints included the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke; first occurrence of the individual components of the primary composite; all-cause mortality; and hospital admissions for congestive heart failure.
After a median follow up of 3 years, sitagliptin, when added to usual care, did not increase the risk of major adverse cardiovascular events or the risk of hospitalisation for heart failure compared to usual care without sitagliptin in patients with type 2 diabetes.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with the reference product containing sitagliptin in one or more subsets of the paediatric population in type 2 diabetes mellitus.

5.2 Pharmacokinetic properties

Absorption

Following 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 post-dose, mean plasma AUC of sitagliptin was 8.52 μM•hr, Cmax was 950 nM. The absolute bioavailability of sitagliptin is approximately 87 %. Since coadministration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics, sitagliptin may be administered with or without food.
Plasma AUC of sitagliptin increased in a dose-proportional manner. Doseproportionality was not established for Cmax and C24hr (Cmax increased in a greater than dose-proportional manner and C24hr increased in a less than dose-proportional manner).

Biotransformation

Sitagliptin is primarily eliminated unchanged in urine, and metabolism is a minor pathway. Approximately 79 % of sitagliptin is excreted unchanged in the urine.

Following a [14C] 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.

In vitro data showed that sitagliptin is not an inhibitor of CYP isozymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6, and is not an inducer of CYP3A4 and CYP1A2.

Distribution

The mean volume of distribution at steady state following a single 100-mg intravenous dose of sitagliptin to healthy subjects is approximately 198 litres.

The fraction of sitagliptin reversibly bound to plasma proteins is low (38 %).

Elimination

Following administration of an oral [14C] sitagliptin dose to healthy subjects, approximately 100 % of the administered radioactivity was eliminated in faeces (13 %) or urine (87 %) within one week of dosing. The apparent terminal t1/2 following a 100mg oral dose of sitagliptin was approximately 12.4 hours. Sitagliptin accumulates only minimally with multiple doses. The renal clearance was approximately 350 ml/min.

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, which may also be involved in mediating the renal elimination of sitagliptin. However, ciclosporin, a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin. Sitagliptin is not a substrate for OCT2 or OAT1 orPEPT1/2 transporters. In vitro, sitagliptin did not inhibit OAT3 (IC50=160 μM) or pglycoprotein (up to 250 μM) mediated transport at therapeutically relevant plasma concentrations. In a clinical study sitagliptin had a small effect on plasma digoxin concentrations indicating that sitagliptin may be a mild inhibitor of p- glycoprotein.

Characteristics in patients

The pharmacokinetics of sitagliptin were generally similar in healthy subjects and in patients with type 2 diabetes.

Renal impairment

A single-dose, open-label study was conducted to evaluate the pharmacokinetics of a reduced dose of sitagliptin (50 mg) in patients with varying degrees of chronic renal impairment compared to normal healthy control subjects. The study included patients with mild, moderate, and severe renal impairment, as well as patients with ESRD on haemodialysis. In addition, the effects of renal impairment on sitagliptin pharmacokinetics in patients with type 2 diabetes and mild, moderate, or

severe renal impairment (including ESRD) were assessed using population pharmacokinetic analyses.
Compared to normal healthy control subjects, plasma AUC of sitagliptin was increased by approximately 1.2-fold and 1.6-fold in patients with mild renal impairment (GFR ≥ 60 to < 90 ml/min) and patients with moderate renal impairment (GFR ≥ 45 to < 60 ml/min), respectively.
Because increases of this magnitude are not clinically relevant, dosage adjustment in these patients is not necessary.
Plasma AUC of sitagliptin was increased approximately 2-fold in patients with moderate renal impairment (GFR ≥ 30 to < 45 ml/min), and approximately 4fold in patients with severe renal impairment (GFR < 30 ml/min), including in patients with ESRD on haemodialysis. Sitagliptin was modestly removed by haemodialysis (13.5 % over a 3- to 4-hour haemodialysis session starting 4 hours post dose). To achieve plasma concentrations of sitagliptin similar to those in patients with normal renal function, lower dosages are recommended in patients with GFR < 45 ml/min.

Hepatic impairment
No dose adjustment for sitagliptin is necessary for patients with mild or moderate hepatic impairment (Child-Pugh score ≤ 9). 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
No dose adjustment is required based on age. Age did not have a clinically meaningful impact on the pharmacokinetics of sitagliptin based on a population pharmacokinetic analysis of Phase I and Phase II data. Elderly subjects (65 to 80 years) had approximately 19 % higher plasma concentrations of sitagliptin compared to younger subjects.

Paediatric
No studies with sitagliptin have been performed in paediatric patients.
Other patient characteristics
No dose adjustment is necessary based on gender, race, or body mass index (BMI). These characteristics had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data.

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-week rat 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 approximately 23 times the human exposure level. A noeffect 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

1.Microcrystalline Cellulose PH 101
2. Anhydrous Calcium hydrogen Phosphate
3. Povidone (K-30)
4.Isopropyl Alcohol
5.Croscarmellose Sodium
6. Sodium stearyl fumarate
7. Magnesium Stearate
8. Instamoistshield AQ-II White A22R01100
9. Purified Water.

6.2. Incompatibilities

None.

6.3. Shelf life

02 Years

6.4. Special precautions for Storage

Store below 30°C. Protect from light and moisture.

6.5. Nature and Contents of container

10 Tablets packed in Alu-Alu Blister, such 03 blisters of 30 tablets packed in a carton with a leaflet.

6.6 Special precautions for disposal and other handling

- None

7. APPLICANT:
ZIFAM PINNACLE NIGERIA LTD, ILUPEJU BYPASS
BESIDE FIRST BANK ILUPEJU MUSHIN LAGOS

MANUFACTURING SITE
M/s. Delta Biopharma Private Limited,
Plot. No.58, Block-C, Industrial Park, Menakuru Village, Naidupeta Mandal,
Tirupati District – 524 126, Andhra Pradesh, India.
Telephone: +912269774400 E-Mail: info@deltabiopharma.co.in

8. MARKETING AUTHORIZATION NUMBERS
Nil

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION
Nil

10. DATE OF REVISION OF TEXT
Nil