PACKAGE INSERT

1. NAME OF THE MEDICINAL PRODUCT

Zyglip Film Coated Tablet 50mg
Zyglip Film Coated Tablet 100mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Zyglip Film Coated Tablet 50mg
Each film coated tablet contains 50mg of Sitagliptin.

Zyglip Film Coated Tablet 100mg
Each film coated tablet contains 100mg of Sitagliptin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Zyglip Film Coated Tablet 50mg
Pink, round, biconvex, film-coated tablets debossed with "SN" on one side and "50" on the other side.

Zyglip Film Coated Tablet 100mg
Brown, round, biconvex, film-coated tablets debossed with "SN" on one side and "100" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Monotherapy
Zyglip is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus.

Combination with metformin
Zyglip is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin as initial therapy or when the single agent alone, with diet and exercise, does not provide adequate glycemic control. Initial combination therapy or maintenance of combination therapy may not be appropriate for all patients. These management options are left to the discretion of the health care provider.

Combination with a sulphonylurea
Zyglip is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with a sulphonylureas when treatment with maximal tolerated dose of sulphonylurea alone, with diet and exercise, does not provide adequate glycemic control and when metformin is inappropriate due to contraindications or intolerance.

Combination with metformin and a sulphonylurea
Zyglip is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin and a sulphonylurea when dual therapy with these two agents and with diet and exercise does not provide adequate glycemic control.

Combination with a peroxisome proliferator-activated receptor gamma (PPARγ) agonist
Zyglip is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with a PPARγ agonist (i.e. thiazolidinediones) when diet and exercise, plus the single agent do not provide adequate glycemic control.

Combination with metformin and a PPARγ agonist
Zyglip is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin and a PPARγ agonist (i.e., thiazolidinediones) when dual therapy with these agents, with diet and exercise, does not provide adequate glycemic control.

Combination with Insulin
Zyglip is indicated in patients with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycemic control in combination with insulin (with or without metformin).

4.2 Posology and method of administration

The recommended dose of Zyglip is 100 mg once daily as monotherapy or as combination therapy with metformin, a sulfonylurea, insulin (with or without metformin), a PPARγ agonist (i.e., thiazolidinediones), metformin plus a sulfonylurea, or metformin plus a PPARγ agonist. Zyglip can be taken with or without food.

When Zyglip 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 hypoglycaemia (see section 4.4, *Hypoglycemia in Combination with a Sulfonylurea or with Insulin*).

Patients with Renal Impairment
Because there is a dosage adjustment based upon renal function, assessment of renal function is recommended prior to initiation of Zyglip and periodically thereafter. For patients with mild renal impairment (estimated glomerular filtration rate [eGFR] ≥ 60 mL/min/1.73m^2 to < 90 mL/min/1.73m^2), no dosage adjustment for Zyglip is required.

For patients with moderate renal impairment (eGFR≥45mL/min/1.73 m^2 to <60 mL/min/1.73m^2), no dosage adjustment for Zyglip is required.

For patients with moderate renal impairment (eGFR≥30 mL/min/1.73 m^2 to <45 mL/min/1.73m^2), the dose of Zyglip is 50 mg once daily.

For patients with severe renal impairment (eGFR ≥ 15 mL/min/1.73m^2 to < 30 mL/min/1.73m^2) or with end-stage renal disease (ESRD) (eGFR < 15 mL/min/1.73m^2), including those requiring hemodialysis or peritoneal dialysis, the dose of sitagliptin is 25mg once daily. Sitagliptin may be administered without regard to the timing of dialysis.

Pediatric population
Zyglip should not be used in children and adolescents 10 to 17 years of age because of insufficient efficacy. Zyglip has not been studied in pediatric patients under 10 years of age.

Elderly
No dose adjustment is necessary based on age

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. Nevertheless, Sitagliptin is primarily renally eliminated, severe hepatic impairment is not expected to affect the pharmacokinetic of Sitagliptin.

Note: Zyglip Film coated tablet is not able to deliver all approved dose regimens of Sitagliptin. Therefore, other approved strengths of Sitagliptin tablet should be used in such cases.

4.3 Contraindications

Zyglip is contraindicated in patients who are hypersensitive to any components of this product (see section 4.4, *Hypersensitivity Reactions* and section 4.8, *Post-Marketing Experience*).

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.

Pancreatitis: There have been reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis (see section 4.8), in patients taking sitagliptin. 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. If pancreatitis is suspected, sitagliptin and other potentially suspect medicinal products should be discontinued

Use in Patients with 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 eGFR< 45 mL/min/1.73 m^2, as well as in ESRD patients requiring hemodialysis or peritoneal dialysis (see section 4.2, *Patients with Renal Impairment*).

Use in the elderly: No dosage adjustment is required based on age. Elderly patients are more likely to have renal

impairment; as with other patients, dosage adjustment may be required in the presence of significant renal impairment.

Hypoglycemia in Combination with a Sulfonylurea or with Insulin: In clinical trials of sitagliptin as monotherapy and sitagliptin as part of combination therapy with agents not known to cause hypoglycemia (i.e., metformin or a PPARγ agonist (thiazolidinedione), rates of hypoglycemia reported with sitagliptin were similar to rates in patients taking placebo. As is typical with other antihyperglycemic agents, hypoglycemia has been observed when sitagliptin was used in combination with insulin or a sulfonylurea (see section 4.8). Therefore, to reduce the risk of sulfonylurea- or insulin-induced hypoglycemia, a lower dose of sulfonylurea or insulin may be considered (see section 4.2).

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. 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. 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 (see section 4.3 and section 4.8, *Post-marketing Experience*).

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 DPP-4 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.

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

4.5 Interaction with other medicinal products and other forms of interaction

In drug interaction studies, sitagliptin did not have clinically meaningful effects on the pharmacokinetics of the following: metformin, rosiglitazone, glyburide, simvastatin, warfarin, and oral contraceptives. Based on these data, sitagliptin does not inhibit CYP isozymes CYP3A4, 2C8, or 2C9. Based on in vitro data, sitagliptin is also not expected to inhibit CYP2D6, 1A2, 2C19 or 2B6 or to induce CYP3A4.

Co-administration of multiple twice-daily doses of metformin with sitagliptin did not meaningfully alter the pharmacokinetics of sitagliptin in patients with type 2 diabetes.

Population pharmacokinetic analyses have been conducted in patients with type 2 diabetes. Concomitant medications did not have a clinically meaningful effect on the pharmacokinetics of sitagliptin. Medications assessed were those that are commonly administered to patients with type 2 diabetes including cholesterol-lowering agents (e.g., statins, fibrates, ezetimibe), antiplatelet agents (e.g., clopidogrel), antihypertensives (e.g., ACE inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, hydrochlorothiazide), analgesics and nonsteroidal anti-inflammatory agents (e.g., naproxen, diclofenac, celecoxib), anti-depressants (e.g., bupropion, fluoxetine, sertraline), antihistamines (e.g., cetirizine), proton-pump inhibitors (e.g., omeprazole, lansoprazole), and medications for erectile dysfunction (e.g., sildenafil).

There was a slight increase in the area under the curve (AUC, 11%) and mean peak drug concentration (C_{max}, 18%) of digoxin with the co-administration of sitagliptin. These increases are not considered to be clinically meaningful. Patients receiving digoxin should be monitored appropriately. No dosage adjustment of digoxin or sitagliptin is recommended.

The AUC and C_{max} of sitagliptin were increased approximately 29% and 68%, respectively, in subjects with co-administration of a single 100 mg oral dose of sitagliptin and a single 600 mg oral dose of cyclosporine, a potent probe inhibitor of p-glycoprotein. The observed changes in sitagliptin pharmacokinetics are not considered to be clinically meaningful. No dosage adjustment for sitagliptin is recommended when co-administered with cyclosporine or other p-glycoprotein inhibitors (e.g., ketoconazole).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate and well-controlled studies in pregnant women; therefore, the safety of sitagliptin in pregnant women is not known. sitagliptin, like other oral antihyperglycemic agents, is not recommended for use in pregnancy.

Lactation
Sitagliptin is secreted in the milk of lactating rats. It is not known whether sitagliptin is secreted in human milk. Therefore, sitagliptin should not be used by a woman who is nursing.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Add-on Combination with a Sulfonylurea:
The drug-related adverse reaction reported in patients was hypoglycemia.

Add-on Combination with Metformin and a PPAR γ Agonist:
The drug-related adverse reactions reported in patients were headache, diarrhea, nausea, hypoglycemia, vomiting, upper respiratory tract infection, cough, fungal skin infection and peripheral edema.

Initial Combination Therapy with Metformin:
The drug-related adverse reactions reported in patients were diarrhea, dyspepsia, flatulence, vomiting and headache.

Initial Combination Therapy with a PPAR γ Agonist:
The only drug-related adverse reaction reported in patients was decreased blood glucose.

Add-on Combination with Insulin:
The drug-related adverse reactions reported in patients were hypoglycemia, influenza and headache.

Post-marketing experience:
Additional adverse reactions have been identified during post-marketing 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 (see section 4.3 and 4.4, *Hypersensitivity Reactions*); acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis (see section 4.4, *Pancreatitis*); worsening renal function, including acute renal failure (sometimes requiring dialysis); bullous pemphigoid (see section 4.4, *Bullous Pemphigoid*); severe and disabling arthralgia (see section 4.4, *Severe and Disabling Arthralgia*); upper respiratory tract infection; nasopharyngitis; constipation; vomiting; headache; myalgia; pain in extremity; back pain; pruritus; thrombocytopenia.

Laboratory test findings:
The incidence of laboratory adverse experiences was similar in patients treated with sitagliptin 100 mg compared to patients treated with placebo. Across clinical studies, a small increase in white blood cell count (approximately 200 cells/microL difference in WBC vs placebo; mean baseline WBC approximately 6600 cells/microL) was observed due to an increase in neutrophils.
This observation was seen in most but not all studies. This change in laboratory parameters is not considered to be clinically relevant.

4.9 Overdose

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 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

5.1 Pharmacodynamic properties

General
In patients with type 2 diabetes, administration of single oral doses of sitagliptin leads to inhibition of DPP-4 enzyme activity for a 24-hour period, resulting in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, increased plasma levels of insulin and C-peptide, decreased glucagon concentrations, reduced fasting glucose, and reduced glucose excursion following an oral glucose load or a meal.

Mechanism of Action
Sitagliptin is a member of a class of oral anti-hyperglycemic agents called dipeptidyl peptidase 4 (DPP-4) inhibitors, which improve glycemic control in patients with type 2 diabetes by enhancing the levels of active incretin 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. 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. 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 hypoglycemia. The activity of GLP-1 and GIP is limited by the DPP-4 enzyme, which rapidly hydrolyzes 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 hyperglycemia, these changes in insulin and glucagon levels lead to lower hemoglobin A1c (HbA1c) and lower fasting and post-prandial glucose concentrations. The glucose-dependent mechanism of sitagliptin is distinct from the mechanism of sulfonylureas, which increase insulin secretion even when glucose levels are low and can lead to hypoglycemia 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.

5.2 Pharmacokinetic properties

The pharmacokinetics of sitagliptin have been extensively characterized in healthy subjects and patients with type 2 diabetes. After oral administration of a 100mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median Tmax) occurring 1 to 4 hours post-dose. Plasma AUC of sitagliptin increased in a dose-proportional manner. Following a single oral 100-mg dose to healthy volunteers, mean plasma AUC of sitagliptin was 8.52 μM•hr, C_{max} was 950 nM, and apparent terminal half-life ($t_{1/2}$) was 12.4 hours. Plasma AUC of sitagliptin 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 were generally similar in healthy subjects and in patients with type 2 diabetes.

Absorption
The absolute bioavailability of sitagliptin is approximately 87%. Since co-administration of a high fat meal with sitagliptin had no effect on the pharmacokinetics, sitagliptin may be administered with or without food.

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

Metabolism
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 [^{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
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. The apparent terminal $t_{1/2}$ following a 100-mg oral dose of sitagliptin was approximately 12.4 hours and 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, cyclosporine, a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin.

Characteristics in Patients
Renal Impairment: Plasma AUC of sitagliptin was increased approximately 2-fold in patients with moderate renal impairment (eGFR ≥ 30 mL/min/1.73 m^2 to < 45 mL/min/1.73m^2), and approximately 4-fold in patients with severe renal impairment (eGFR < 30 mL/min/1.73m^2), including patients with ESRD on hemodialysis. Sitagliptin was modestly removed by hemodialysis (13.5% over a 3- to 4-hour hemodialysis 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 eGFR <45 mL/min/1.73m^2 (see section 4.2, *Patients with Renal Impairment*).

Hepatic Impairment: In patients with moderate hepatic impairment (Child-Pugh score 7 to 9), mean AUC and C_{max} of sitagliptin increased approximately 21% and 13%, respectively, compared to healthy matched controls following administration of a single 100mg dose of sitagliptin. These differences are not considered to be clinically meaningful. No dosage adjustment for sitagliptin is necessary for patients with mild or moderate hepatic impairment.

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 dosage 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. Elderly subjects (65 to 80 years) had approximately 19% higher plasma concentrations of sitagliptin compared to younger subjects.

Pediatric: The pharmacokinetics of sitagliptin (single dose of 50mg, 100mg or 200mg) were investigated in pediatric patients (10 to 17 years of age) with type 2 diabetes. In this population, the dose-adjusted AUC of sitagliptin in plasma was approximately 18% lower compared to adult patients with type 2 diabetes for a 100 mg dose. This is not considered to be a clinically meaningful difference based on the flat PK/PD relationship between the dose of 50mg and 100mg in adults.

No studies with sitagliptin have been performed in pediatric patients < 10 years of age.

Gender: No dosage adjustment is necessary based on gender. Gender had no clinically meaningful effect on the pharmacokinetics of sitagliptin.

Race: No dosage adjustment is necessary based on race. Race had no clinically meaningful effect on the pharmacokinetics of sitagliptin.

Body Mass Index (BMI): No dosage adjustment is necessary based on BMI. Body mass index had no clinically meaningful effect on the pharmacokinetics of sitagliptin.

Type 2 Diabetes: The pharmacokinetics of sitagliptin in patients with type 2 diabetes are generally similar to those in healthy subjects.

7. PHARMACEUTICAL PARTICULARS

7.1 List of Excipients

Calcium Hydrogen Phosphate Anhydrous
Microcrystalline cellulose
Croscarmellose sodium
Low-Substituted Hydroxypropyl Cellulose
Colloidal Silicon Dioxide
Magnesium stearate
Sodium stearyl fumarate

Film coating
Hydroxypropylmethyl cellulose
Hydroxypropylcellulose
Polyethylene glycol
Titanium dioxide
Ferric oxide, yellow
Ferric oxide, red
Ferric oxide, black (100mg)
Talc

7.2 Incompatibilities

Not applicable.

7.3 Shelf life

Please refer to the outer carton.

7.4 Special precautions for storage

Store below 30ºC.

8. DOSAGE FORM AND PACKAGING AVAILABLE

Zyglip is available in 14's and 28's pack size.

Zyglip Film Coated Tablets 50mg and 100mg will be packed in PVC/PVDC or Alu-Alu blisters. Blisters are packed into outer carton with 1 physicians leaflet.

Not all registered pack sizes are marketed.

9. MANUFACTURER

Sandoz Private Limited
Plot No. 8-A/2 and 8-B, TTC Industrial Area, Kalwe Block,
Village Dighe, Thane, 400708, India.

10. DATE OF REVISION OF THE TEXT

PI version: October 2026

*Package insert will be presented in font size 10, measure in Times New Roman *(this statement is for registration purpose only)*