Professional Information for GLIZEB

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

GLIZEB 25 film-coated tablets

GLIZEB 50 film-coated tablets

GLIZEB 100 film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

GLIZEB 25: Each film-coated tablet 25 mg sitagliptin.

GLIZEB 50: Each film-coated tablet 50 mg sitagliptin.

GLIZEB 100: Each film-coated tablet 100 mg sitagliptin.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

GLIZEB 25: White to off-white, round, biconvex, film-coated tablets, debossed with ‘12’ on one side and ‘40’ on the other side.

GLIZEB 50: Pale yellow coloured, round, biconvex, film-coated tablets, debossed with ‘12’ on one side and ‘41’ on the other side.

GLIZEB 100: Beige coloured, round, biconvex, film-coated tablets, debossed with ‘12’ on one side and ‘42’ on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Monotherapy

GLIZEB is indicated as an adjunct to diet and exercise to improve glycaemic control in adult patients with type 2 diabetes mellitus.

Combination therapy

GLIZEB is also indicated in patients with type 2 diabetes mellitus to improve glycaemic control in combination with metformin or a peroxisome proliferator-activated receptor gamma PPAR*γ* agonist (e.g. thiazolidinedione) when diet and exercise, plus the single medicine do not provide adequate glycaemic control.

The combination of **GLIZEB** and sulphonylureas has not been adequately studied.

4.2 Posology and method of administration

Posology

The dose of **GLIZEB** in combination with metformin or a PPAR*γ* agonist is 100 mg once daily. The dosage of metformin or PPAR*γ* agonist should be maintained, and **GLIZEB** administered concomitantly.

If a dose of **GLIZEB** is missed, it should be taken as soon as the patient remembers. A double dose of **GLIZEB** should not be taken on the same day.

Patients with renal insufficiency

For patients with mild renal insufficiency (creatinine clearance (CrCl) ≥ 50 mL/min, approximately corresponding to serum creatinine levels of ≤ 150 µmol/L in men and ≤ 133 µmol/L in women), no dosage adjustment for **GLIZEB** is required.

For patients with moderate renal insufficiency (CrCl ≥ 30 to ≤ 50 mL/min, approximately corresponding to serum creatinine levels of > 150 µmol/L to < 265 µmol/L in men and

> 133 µmol/L to not < 221 µmol/L in women), the dose of **GLIZEB** is 50 mg once daily. This dose should be decreased if CrCl decreases to < 30 mL/min.

For patients with severe renal insufficiency (CrCl < 30 mL/min, approximately corresponding to serum creatinine levels of > 265 µmol/L in men and > 221 µmol/L in women) or with end-stage renal disease requiring haemodialysis, the dose of **GLIZEB** is 25 mg once daily.

GLIZEB may be administered without regard to the timing of haemodialysis.

Patients with hepatic insufficiency:

No dosage adjustment is necessary for patients with mild to moderate hepatic insufficiency.

GLIZEB has not been studied in patients with severe hepatic insufficiency (see section 4.3).

Elderly patients:

No dosage adjustment is necessary for elderly patients.

Paediatric population:

There are no data available on the use of **GLIZEB** in patients younger than 18 years of age.

Therefore, use of **GLIZEB** in paediatric patients is not recommended.

Method of administration

Oral use.

GLIZEB can be taken with or without food.

4.3 Contraindications

- Hypersensitivity to sitagliptin or to any of the excipients listed in section 6.1;
- A history of severe hypersensitivity reaction, such as anaphylaxis or angioedema to **GLIZEB** or any other gliptins (DPP-4) (see section 4.4);
- **GLIZEB** has not been studied in patients with severe hepatic insufficiency (see section 5.2).

4.4 Special warnings and precautions for use

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, GLIZEB should be discontinued immediately. Other potential causes for the event should be assessed, and alternative treatment for diabetes initiated (see section 4.3).

Diabetes

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

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 **GLIZEB** (with or without supportive treatment), but very rare cases of necrotising or haemorrhagic pancreatitis and/or death have been reported (see section 4.8). If pancreatitis is suspected, **GLIZEB** and other potentially suspect medicines should be discontinued; if acute pancreatitis is confirmed, **GLIZEB** should not be restarted.

Caution should be exercised in patients with a history of pancreatitis.

Hypoglycaemia when used in combination with other anti-hyperglycaemic medicines

In clinical trials of **GLIZEB** as monotherapy and as part of combination therapy with medicines not known to cause hypoglycaemia (i.e. metformin and/or 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 (see section 4.2).

Renal impairment

GLIZEB is renally excreted. A dosage adjustment is recommended in patients with moderate or severe renal impairment, and in patients with end-stage renal disease requiring haemodialysis or peritoneal dialysis. To achieve plasma concentrations of sitagliptin similar to those in patients with normal renal function, lower doses of **GLIZEB** are recommended in patients with glomerular filtration rate (GFR) < 45 mL/min, as well as in end stage renal disease (ESRD) patients requiring haemodialysis or peritoneal dialysis (see section 4.2 and 5.2).

When considering the use of **GLIZEB** in combination with another anti-diabetic medicine, its conditions for use in patients with renal impairment should be checked.

Bullous pemphigoid

There have been reports of bullous pemphigoid in patients taking DPP-4 inhibitors including sitagliptin. **GLIZEB** should be discontinued if bullous pemphigoid is suspected.

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines on GLIZEB

Clinical data suggest that the risk for clinically meaningful interactions by co-administered medicines discussed below 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 **GLIZEB**.

Metabolism may play a more significant role in the elimination of **GLIZEB** 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 **GLIZEB** in patients 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 p-glycoprotein 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*.

Metformin

Co-administration of multiple twice-daily doses of 1 000 mg metformin with 50 mg **GLIZEB** did not meaningfully alter the pharmacokinetics of **GLIZEB** in patients with type 2 diabetes.

Ciclosporin

A study was conducted to assess the effect of ciclosporin, a potent inhibitor of p-glycoprotein, on the pharmacokinetics of sitagliptin. Co-administration of a single 100 mg oral dose of **GLIZEB** and a single 600 mg oral dose of ciclosporin increased the area under the curve (AUC) and peak concentration (C_{max}) of **GLIZEB** by approximately 29 % and 68 %, respectively. These changes in **GLIZEB** pharmacokinetics were not considered to be clinically meaningful. The renal clearance of **GLIZEB** was not meaningfully altered. Therefore, meaningful interactions would not be expected with ciclosporin or other p-glycoprotein inhibitors (e.g. ketoconazole).

Effects of GLIZEB on other medicines

Digoxin

GLIZEB 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 area under the curve (AUC) of digoxin was increased on average by 11 %, and the plasma peak concentration (C_{max}) on average by 18 %. No dose adjustment of digoxin or **GLIZEB** is recommended. However,

patients at risk of digoxin toxicity should be monitored for this when **GLIZEB** and digoxin are administered concomitantly.

Other medicines

In vitro data suggest that **GLIZEB** does not inhibit nor induce CYP450 isoenzymes. In interaction studies, sitagliptin did not meaningfully alter the pharmacokinetics of metformin, 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). **GLIZEB** may be a mild inhibitor of p-glycoprotein *in vivo*.

Based on *in vitro* data, **GLIZEB** is also not expected to inhibit CYP2D6, 1A2, C19 or 2B6, or to induce CYP3A4. There is limited information on multiple dose co-administration of these medicines.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of **GLIZEB** in pregnant women. **GLIZEB** should not be used during pregnancy.

Lactation

It is unknown whether **GLIZEB** is excreted in human breast milk. **GLIZEB** should not be used during breastfeeding.

Fertility

Animal data do not suggest an effect of **GLIZEB** on male and female fertility. Human data are lacking (see section 5.3).

4.7 Effects on ability to drive and use machines

GLIZEB 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 with the use of **GLIZEB** and caution is advised until the effects of **GLIZEB** are known.

In addition, patients should be alerted to the risk of hypoglycaemia when **GLIZEB** 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 with the use of **GLIZEB**. Hypoglycaemia has been reported in combination with sulphonylurea (4,7 %-13,8 %) and insulin (9,6 %) (see section 4.4).

Table 1: Adverse reactions of GLIZEB monotherapy

Adverse reaction	**Frequency of adverse reaction**
Blood and the lymphatic system disorders	
thrombocytopenia	*less frequent*
Immune system disorders	
*[#]hypersensitivity reactions, including anaphylactic responses	*frequency not known*
*angioedema	*frequency not known*
Metabolism and nutrition disorders	
[#]hypoglyceamia	*frequent*
Nervous system disorders	
headache	*frequent*
dizziness	*less frequent*
Respiratory, thoracic and mediastinal disorders	

*interstitial lung disease	*frequency not known*
#nasopharyngitis	*frequency not known*
#upper respiratory tract infection	*frequency not known*
Gastrointestinal disorders	
constipation	*less frequent*
*vomitting	*frequency not known*
*#acute pancreatitis	*frequency not known*
*#fatal and non-fatal haemorrhagic and necrotising pancreatitis	*frequency not known*
Skin and subcutaneous tissue disorders	
*pruritus	*frequency unknown*
*#rash	*frequency not known*
*#urticaria	*frequency not known*
*#cutaneous vasculitits	*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	
*impaired renal function	*frequency not known*
*acute renal failure	*frequency not known*

* Adverse reactions were identified post-marketing.

See section 4.4.

Description of selected adverse reactions

In addition to the adverse reactions described above, adverse reactions reported regardless of causal relationship to medicine and occurring in at least 5 % and more commonly in patients treated with **GLIZEB** included upper respiratory tract infection and nasopharyngitis. Additional adverse reactions reported regardless of causal relationship to medicine that occurred more frequently in patients treated with **GLIZEB** (not reaching the 5 % level, but occurring with an incidence of > 0,5 % higher with **GLIZEB** 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 **GLIZEB** with other antidiabetic medicines than in studies of **GLIZEB** monotherapy. These included hypoglycaemia (occurring frequently with the combination of sulphonylurea and metformin), influenza (occurring frequently with insulin (with or without metformin)), nausea and vomiting (occurring frequently with metformin), flatulence (occurring frequently with metformin or pioglitazone), constipation (occurring frequently with the combination of sulphonylurea and metformin), peripheral oedema (occurring frequently with pioglitazone or the combination of pioglitazone and metformin), somnolence and diarrhoea (occurring less frequently with metformin), and dry mouth (occurring less frequently with insulin (with or without metformin)).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of **GLIZEB** is important. It allows continued monitoring of the benefit/risk balance of **GLIZEB**. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

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.

GLIZEB is modestly dialysable. Prolonged haemodialysis may be considered if clinically appropriate. It is not known if **GLIZEB** is dialysable by peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 21.2 Oral hypoglyceamics

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 medicines called dipeptidyl peptidase 4 (DPP-4) inhibitors. The improvement in glycaemic control observed with sitagliptin may be mediated 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 hypoglycaemia. 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 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.

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 T_{max}) occurring 1 to 4 hours post-dose, mean plasma AUC of sitagliptin was 8,52 micromolar hours, C_{max} was 950 nM.

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

Plasma AUC of sitagliptin increased in a dose-proportional manner. Dose-proportionality was not established for C_{max} and C_{24hr} (C_{max} increased in a greater than dose-proportional manner and

C_{24hr} increased in a less than doseproportional manner).

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 %).

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 ^{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.

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.

Elimination

Following administration of an oral ^{14}C sitagliptin dose to healthy subjects, approximately 100 % of the administered radioactivity was eliminated in faeces or urine within one week of dosing. The apparent terminal $t_{1/2}$ following a 100-mg 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 or $PEPT_{1/2}$ transporters. *In vitro*, sitagliptin did not inhibit OAT3 (IC50=160 µM) or p-glycoprotein (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.

Special populations

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 4-fold 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 (see section 4.2).

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).

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 of age) had higher plasma concentrations of sitagliptin compared to younger subjects.

Paediatric

No studies have been performed in paediatric patients.

Other

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 pharmacokinetic and population pharmacokinetic analysis data.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Colloidal silicon dioxide (E551)

Croscarmellose sodium (E468)

Dibasic calcium phosphate (E341)

Magnesium stearate (E572)

Malic acid (E296)

Microcrystalline cellulose (E460)

Povidone (E1201)

Film-coating:

GLIZEB 25:

Opadry white (containing macrogol (E1521), polyvinyl alcohol (E1203), talcum (E553b), titanium dioxide (E171))

GLIZEB 50:

Opadry yellow (containing ferrosoferric oxide (E172), iron oxide yellow (E172), macrogol (E1521), polyvinyl alcohol (E1203), talcum (E553b), titanium dioxide (E171))

GLIZEB 100:

Opadry beige (containing FD&C yellow (E110), iron oxide yellow (E172), macrogol (E1521), polyvinyl alcohol (E1203), talcum (E553b), titanium dioxide (E171))

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blister strips in the outer carton until required for use.

6.5 Nature and contents of container

Aluminium/aluminium blister strip containing 10 film-coated tablets packed into an outer carton.

Pack size: 30 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Zydus Healthcare SA (Pty) Ltd

Southdowns Office Park

Building B, Ground Floor

22 Karee Street

Centurion, Pretoria

0157

8. REGISTRATION NUMBERS

GLIZEB 25: 55/21.2/0043

GLIZEB 50: 55/21.2/0044

GLIZEB 100: 55/21.2/0045

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13 September 2022

10. DATE OF REVISION OF THE TEXT