

# Glipita<sup>®</sup>

Sitagliptin  
50 mg and 100 mg Tablet

## Description

Glipita<sup>®</sup> is a preparation of Sitagliptin Phosphate. Sitagliptin Phosphate is an orally-active, potent, and highly selective inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme for the treatment of type 2 diabetes.

## Mode of Action

The DPP-4 inhibitors are a class of agents that act as incretin enhancers. By inhibiting the DPP-4 enzyme, Sitagliptin increases the levels of two known active incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). 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. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. This mechanism is unlike the mechanism seen with sulfonylureas; sulfonylureas cause insulin release even when glucose levels are low, which can lead to sulfonylurea-induced hypoglycemia in patients with type II diabetes and in normal subjects. Sitagliptin demonstrates high selectivity for DPP-4 and does not inhibit closely-related enzymes DPP-8 or DPP-9 at therapeutic concentrations.

## Indications

### Monotherapy

Glipita<sup>®</sup> is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type II diabetes mellitus.

### Combination with Metformin

Glipita<sup>®</sup> 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.

### Combination with a Sulfonylurea

Glipita<sup>®</sup> is indicated in patients with type II diabetes mellitus to improve glycemic control in combination with a sulfonylurea when treatment with the single agent alone, with diet and exercise, does not provide adequate glycemic control.

### Combination with a Thiazolidinediones

Glipita<sup>®</sup> is indicated in patients with type II diabetes mellitus to improve glycemic control in combination with a thiazolidinedione when treatment with the single agent alone, with diet and exercise, does not provide adequate glycemic control.

### Combination with Metformin and a Sulfonylurea

Glipita<sup>®</sup> is indicated in patients with type II diabetes mellitus to improve glycemic control in combination with Metformin and a sulfonylurea when dual therapy with these agents, with diet and exercise, does not provide adequate glycemic control.

## Dosage and Administration

The recommended dose of Sitagliptin is 100 mg once daily as monotherapy or as combination therapy with Metformin, a sulfonylurea, a thiazolidinedione, or Metformin plus a sulfonylurea. Sitagliptin can be taken with or without food. Patients with

### Elderly

No dosage adjustment is necessary for elderly patients.

### Pediatric use

There is no data on use of Sitagliptin in patients younger than 18 years of age and therefore not recommended.

### Renal Insufficiency

For patients with **mild renal insufficiency** (creatinine clearance [CrCl] >50 mL/min, approximately corresponding to serum creatinine levels of >1.7 mg/dL in men and >1.5 mg/dL in women), no dosage adjustment for Sitagliptin is required. In **moderate renal insufficiency** (CrCl >30 to <50 mL/min, approximately

corresponding to serum creatinine levels of >1.7 to <3.0 mg/dL in men and >1.5 to <2.5 mg/dL in women), the dose of Sitagliptin is 50 mg once daily. For patients with **severe renal insufficiency** (CrCl <30 mL/min, approximately corresponding to serum creatinine levels of > 3.0 mg/dL in men and > 2.5 mg/dL in women) 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 hemodialysis.

**Concomitant Use with a Sulfonylurea-** When Sitagliptin is used in combination with a sulfonylurea, a lower dose of sulfonylurea may be required to reduce the risk of hypoglycemia.

### **Hepatic Insufficiency**

No dosage adjustment is necessary for patients with mild to moderate hepatic insufficiency. Sitagliptin has not been studied in patients with severe hepatic insufficiency.

### **Contraindications**

History of a serious hypersensitivity reaction to Sitagliptin, such as anaphylaxis or angioedema.

### **Special Warnings and Precautions**

Sitagliptin should not be used in patients with type I diabetes or for the treatment of diabetic ketoacidosis. Dosage adjustment is recommended in patients with moderate or severe renal insufficiency and in patients with ESRD. Assessment of renal function is recommended prior to initiating Sitagliptin and periodically thereafter. When used with a sulfonylurea, a lower dose of sulfonylurea may be required to reduce the risk of hypoglycemia. There have been post marketing reports of serious allergic and hypersensitivity reactions in patients treated with Sitagliptin such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. In such cases, promptly stop Sitagliptin, assess for other potential causes, and institute appropriate monitoring and treatment, and initiate alternative treatment for diabetes. There have been no clinical studies establishing conclusive evidence of macrovascular risk.

### **Drug Interactions**

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 drug interactions with substrates of CYP3A4, CYP2C8, CYP2C9, and organic cationic transporter (OCT).

#### **Digoxin**

Sitagliptin had a minimal effect on the pharmacokinetics of digoxin. Following administration of 0.25 mg digoxin concomitantly with 100 mg of Sitagliptin daily for 10 days, the plasma AUC of digoxin was increased by 11%, and the plasma C<sub>max</sub> by 18%

#### **Metformin**

Coadministration of multiple twice-daily doses of Sitagliptin with metformin, an OCT substrate, did not meaningfully alter the pharmacokinetics of metformin in patients with type 2 diabetes. Therefore, Sitagliptin is not an inhibitor of OCT-mediated transport.

#### **Sulfonylureas**

Single-dose pharmacokinetics of glyburide, a CYP2C9 substrate, was not meaningfully altered in subjects receiving multiple doses of Sitagliptin. Clinically meaningful interactions would not be expected with other sulfonylureas (e.g., glipizide, tolbutamide, and glimepiride) which, like glyburide, are primarily eliminated by CYP2C9.

#### **Simvastatin**

Single-dose pharmacokinetics of simvastatin, a CYP3A4 substrate, was not meaningfully altered in subjects receiving multiple daily doses of Sitagliptin. Therefore, Sitagliptin is not an inhibitor of CYP3A4-mediated metabolism.

## Thiazolidinediones

Single-dose pharmacokinetics of rosiglitazone was not meaningfully altered in subjects receiving multiple daily doses of Sitagliptin, indicating that Sitagliptin is not an inhibitor of CYP2C8-mediated metabolism.

**Warfarin:** Multiple daily doses of Sitagliptin did not meaningfully alter the pharmacokinetics, as assessed by measurement of S(-) or R(+) warfarin enantiomers, or pharmacodynamics (as assessed by measurement of prothrombin INR) of a single dose of warfarin. Because S(-) warfarin is primarily metabolized by CYP2C9, these data also support the conclusion that Sitagliptin is not a CYP2C9 inhibitor.

## Oral Contraceptives

Co-administration with Sitagliptin did not meaningfully alter the steady-state pharmacokinetics of norethindrone or ethinyl estradiol.

## Cyclosporine

A study was conducted to assess the effect of cyclosporine, a potent inhibitor of p-glycoprotein, on the pharmacokinetics of Sitagliptin. Co-administration of a single 100 mg oral dose of Sitagliptin and a single 600 mg oral dose of cyclosporine increased the AUC and C<sub>max</sub> of Sitagliptin by approximately 29% and 68%, respectively.

These modest changes in Sitagliptin pharmacokinetics were not considered to be clinically meaningful. The renal clearance of Sitagliptin was also not meaningfully altered. Therefore, meaningful interactions would not be expected with other p-glycoprotein inhibitors.

## Use during Pregnancy and Lactation

### Pregnancy category B.

Sitagliptin should be used during pregnancy only if clearly needed. Safety and effectiveness of this combination in pediatric patients & nursing mother have not been established.

## Adverse Effects

Adverse reactions reported in 5% of patients treated with Sitagliptin and more commonly than in patients treated with placebo are: upper respiratory tract infection, nasopharyngitis and headache. Hypoglycemia was also reported more commonly in patients treated with the combination of Sitagliptin and sulfonylurea, with or without Metformin, than in patients given the combination of placebo and sulfonylurea, with or without Metformin.

## 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 hemodialysis session. Prolonged haemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialysable by peritoneal dialysis.

## Pharmaceutical Precautions

Keep out of the reach of children. Store below 30°C. Keep in the original package in a cool & dry place in order to protect from light and moisture.

## Commercial Pack

**Glipita® 50 Tablet:** Box containing 10 tablets in 1X10's alu-alu form pack. Each film coated tablet contains Sitagliptin Phosphate INN equivalent to 50 mg of Sitagliptin.

**Glipita® 100 Tablet:** Box containing 10 tablets in 1X10's alu-alu form pack. Each film coated tablet contains Sitagliptin Phosphate INN equivalent to 100 mg of Sitagliptin.



Manufactured by

**BEXIMCO PHARMACEUTICALS LTD.**

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