



## Sitagliptin: a New Class of Oral Drug for Type 2 Diabetes

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### Introduction

Type 2 diabetes is the most common form of the disease, accounting for about 90% to 95 % of all diagnosed cases of diabetes. In type 2 diabetes, the body does not produce enough insulin or the cells ignore the insulin. Over time, high blood sugar levels can increase the risk for serious complications, including heart disease, blindness, nerve damage and kidney damage (1). Any new oral hypoglycemic drug that can increase the control of blood glucose with fewer adverse effects in patients with diabetes may be welcomed. Sitagliptin is the first and only prescription medication in a new class of oral antihyperglycemic agents, which enhance the body's own ability to lower blood glucose when it is elevated (2).

### Mechanism of Action

Sitagliptin prolongs the activity of proteins that increase the release of insulin after blood sugar rises, such as after a meal. Sitagliptin is a selective inhibitor of the enzyme dipeptidyl peptidase-4 (DPP-4), which metabolizes the naturally occurring incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) resulting in enhanced glucose-dependent insulin secretion from the pancreas and decreased hepatic glucose production. Since GLP-1 enhances insulin secretion in the presence of raised blood glucose levels, inhibiting DPP-IV activity will increase and prolong the action of GLP-1 by reducing its rate of inactivation in plasma (3). Sitagliptin reduces hemoglobin A1c (HbA1c), fasting and postprandial glucose by glucose-dependent stimulation of insulin secretion and inhibition of glucagon secretion (4). GLP-1 has other widespread effects including delaying gastric emptying, significantly reducing glucagons levels and possible central effects on the appetite (3).

### Pharmacokinetics

Bioavailability of sitagliptin is approximately 87%. Half-life is between 8-14 hours. It is 38% bound to plasma proteins. It undergoes limited metabolism via CYP3A4 and CYP2C8. Elimination is mainly through urine (5, 6).

### Clinical Use

In October 2006, the U.S. Food and Drug Administration (FDA) approved sitagliptin as monotherapy and as add-on therapy to either of two other types of oral diabetes medications, metformin or thiazolidinediones to improve blood glucose control in patients with type 2 diabetes when diet and exercise are not enough (5). In March, 2007 it was approved in European Union. Sitagliptin is currently approved in 42 countries (7). The recommended dose of sitagliptin is 100 mg once daily. It may be taken with or without food. In April, 2007 FDA approved the combination product of sitagliptin and metformin for type 2 diabetes (8). In clinical trials of 1-year duration, sitagliptin improved glycaemic control by reducing both fasting and postprandial glucose concentrations, leading to clinically meaningful reductions in glycosylated haemoglobin levels. Monotherapy with sitagliptin 100mg daily decreases mean HbA1c by 0.6-0.79% (mean difference from placebo). When used in combination with metformin or pioglitazone, the mean reduction in HbA1c is 0.7% and 0.9% respectively. Sitagliptin is considered to be weight neutral and lipid neutral (4).

### Adverse effects

In clinical trials, sitagliptin demonstrated an overall incidence of side effects comparable to placebo. The most common side effects in studies were upper respiratory tract infection, stuffy or running nose, sore

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throat, headache and diarrhea. The incidence of hypoglycemia with sitagliptin monotherapy was not significantly different than placebo. Pooled data from 2 monotherapy and 2 combination trials show that the incidence of hypoglycemia was 1.2% and 0.9% for sitagliptin 100mg and placebo respectively (4,5).

#### Drug interactions

Sitagliptin plasma concentrations may be increased modestly (approximately 68%), with cyclosporine which is not expected to be clinically important. Digoxin plasma levels may be increased slightly (approximately 18%), no dosage adjustment is recommended. Although sitagliptin is not as likely to cause hypoglycemia as some other oral diabetes medications, be careful while prescribing any other drug that can potentially lower blood sugar, such as: probenecid, nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin or other salicylates, sulfa drugs, a monoamine oxidase inhibitor (MAOI) or beta-blockers (6).

#### Contraindications

It is a pregnancy category B drug. Because there are no adequate, well-controlled studies of sitagliptin in pregnant women, it should be used during pregnancy only if clearly needed. Caution should be exercised with use of sitagliptin in nursing women. Sitagliptin can pass into breast milk and may harm a nursing baby. In children, safety and efficacy not established. Dosage adjustments are needed in patients with moderate or severe renal function impairment. In moderate renal function impairment (Ccr 30 to less than 50 mL/min) dose should be reduced to 50 mg once daily. In severe renal function impairment (Ccr less than 30 mL/min) dose should be reduced to 25 mg once daily. Sitagliptin is also contraindicated in diabetic ketoacidosis (2,4,5).

#### Conclusion

Sitagliptin, an oral dipeptidyl peptidase-4 (DPP-4) reversible inhibitor, improves glycaemic control by inhibiting DPP-4 inactivation of the incretin hormones glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide. This increases active incretin and insulin levels, and decreases glucagon levels and post-glucose-load glucose excursion. Sitagliptin, which can be used as monotherapy or in combination with other antidiabetic drugs, is a promising new treatment option, especially for patients with early-stage type 2 diabetes and more severe hyperglycemia, although experience with this noble drug will further help it to establish its supremacy as oral drug for Type -2 DM.

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