



Dear Doctor:

Thank you for your interest in the enclosed reprint, "Efficacy and Safety of the Dipeptidyl Peptidase-4 Inhibitor, Sitagliptin, in Patients With Type 2 Diabetes Mellitus Inadequately Controlled on Glimepiride Alone or on Glimepiride and Metformin" by K. Hermansen et al, as published in *Diabetes, Obesity and Metabolism*, Volume 9, 2007. The objective of the study was to examine the efficacy and safety of sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, in patients with type 2 diabetes who had inadequate glycemic control ($A1C \geq 7.5\%$ and $\leq 10.5\%$) while on glimepiride with or without metformin.

JANUVIA™ (sitagliptin) is indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus.

JANUVIA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. JANUVIA has not been studied in combination with insulin.

JANUVIA is contraindicated in patients with a history of a serious hypersensitivity reaction to sitagliptin, such as anaphylaxis and angioedema.

A dosage adjustment is recommended in patients with moderate or severe renal insufficiency or with end-stage renal disease requiring hemodialysis or peritoneal dialysis.

As is typical with other antihyperglycemic agents used in combination with a sulfonylurea, when JANUVIA was used in combination with a sulfonylurea, a class of medications known to cause hypoglycemia, the incidence of hypoglycemia was increased over that of placebo. Therefore, a lower dose of sulfonylurea may be required to reduce the risk of hypoglycemia.

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with JANUVIA. 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 JANUVIA, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue JANUVIA, assess for other potential causes for the event, and institute alternative treatment for diabetes.

In clinical studies, the adverse reactions, regardless of investigator assessment of causality, in $\geq 5\%$ of patients treated with JANUVIA as monotherapy and in combination and more commonly than in patients treated with placebo, were upper respiratory tract infection, nasopharyngitis, and headache.

In combination with sulfonylurea and with sulfonylurea and metformin, the adverse reaction of hypoglycemia was also reported more commonly with JANUVIA than with placebo.

Before prescribing JANUVIA, please read the accompanying Prescribing Information. For additional copies of the Prescribing Information, call 1-800-672-6372, visit Januvia.com, or contact your Merck representative.

Thank you for your interest in this information about JANUVIA.

Sincerely,

A handwritten signature in black ink, appearing to read "Bram Greenberg".

Bram Greenberg, MD, FAAP
Executive Director, Medical Services

Enclosures: Prescribing Information for JANUVIA

[Click to view Study Abstract](#)

Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin

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Aim: To assess the efficacy and safety of a 24 week treatment with sitagliptin, a highly selective once daily oral dipeptidyl peptidase 4 (DPP 4) inhibitor, in patients with type 2 diabetes who had inadequate glycaemic control [glycosylated haemoglobin (HbA_{1c}) $\geq 7.5\%$ and $\leq 10.5\%$] while on glimepiride alone or in combination with metformin.

Methods: After a screening, diet/exercise run in and drug wash off period, a glimepiride \pm metformin dose titration/stabilization period and a 2 week, single blind placebo run in, 441 patients (of ages 18–75 years) were randomized to receive the addition of sitagliptin 100 mg once daily or placebo in a 1 : 1 ratio for 24 weeks. Of these patients, 212 were on glimepiride (≥ 4 mg/day) monotherapy and 229 were on glimepiride (≥ 4 mg/day) plus metformin (≥ 1500 mg/day) combination therapy. Patients exceeding pre specified glycaemic thresholds during the double blind treatment period were provided open label rescue therapy (pioglitazone) until study end. The primary efficacy analysis evaluated the change in HbA_{1c} from baseline to Week 24. Secondary efficacy endpoints included fasting plasma glucose (FPG), 2 h post meal glucose and lipid measurements.

Results: Mean baseline HbA_{1c} was 8.34% in the sitagliptin and placebo groups. After 24 weeks, sitagliptin reduced HbA_{1c} by 0.74% ($p < 0.001$) relative to placebo. In the subset of patients on glimepiride plus metformin, sitagliptin reduced HbA_{1c} by 0.89% relative to placebo, compared with a reduction of 0.57% in the subset of patients on glimepiride alone. The addition of sitagliptin reduced FPG by 20.1 mg/dl ($p < 0.001$) and increased homeostasis model assessment β , a marker of β cell function, by 12% ($p < 0.05$) relative to placebo. In patients who underwent a meal tolerance test ($n = 134$), sitagliptin decreased 2 h post prandial glucose (PPG) by 36.1 mg/dl ($p < 0.001$) relative to placebo. The addition of sitagliptin was generally well tolerated, although there was a higher incidence of overall (60 vs. 47%) and drug related adverse experiences (AEs) (15 vs. 7%) in the sitagliptin group than in the placebo group. This was largely because of a higher incidence of hypoglycaemia AEs (12 vs. 2%, respectively) in the sitagliptin group compared with the placebo group. Body weight modestly increased with sitagliptin relative to placebo (+0.8 vs. -0.4 kg; $p < 0.001$).

Conclusions: Sitagliptin 100 mg once daily significantly improved glycaemic control and β cell function in patients with type 2 diabetes who had inadequate glycaemic control with glimepiride or glimepiride plus metformin therapy. The addition of sitagliptin was generally well tolerated, with a modest increase in hypoglycaemia and body weight, consistent with glimepiride therapy and the observed degree of glycaemic improvement.

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