



Dear Doctor:

Thank you for your interest in the enclosed reprint, "Effect of Initial Combination Therapy With Sitagliptin, a Dipeptidyl Peptidase-4 Inhibitor, and Metformin on Glycemic Control in Patients With Type 2 Diabetes," by B.J. Goldstein et al, as published in *Diabetes Care*, Volume 30, Number 8, August 2007. The objective of the study was to assess the efficacy and safety of initial combination therapy with sitagliptin and metformin in patients with type 2 diabetes and inadequate glycemic control on diet and exercise.

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.

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, as it would not be effective in these settings. 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 or 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

Enclosure: Prescribing Information for JANUVIA

[Click to view Study Abstract](#)

Effect of Initial Combination Therapy With Sitagliptin, a Dipeptidyl Peptidase-4 Inhibitor, and Metformin on Glycemic Control in Patients With Type 2 Diabetes

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OBJECTIVE — To assess the efficacy and safety of initial combination therapy with sitagliptin and metformin in patients with type 2 diabetes and inadequate glycemic control on diet and exercise.

RESEARCH DESIGN AND METHODS — In a 24-week, randomized, double-blind, placebo-controlled, parallel-group study, 1,091 patients with type 2 diabetes and A1C 7.5–11% were randomized to one of six daily treatments: sitagliptin 100 mg/metformin 1,000 mg (S100/M1000 group), sitagliptin 100 mg/metformin 2,000 mg (S100/M2000 group), metformin 1,000 mg (M1000 group), metformin 2,000 mg (M2000 group) (all as divided doses administered twice daily [b.i.d.]), sitagliptin 100 mg q.d. (S100 group), or placebo. Patients who had an A1C >11% or a fasting glucose value >280 mg/dl after the run-in period were not eligible to be randomized; these patients could participate in an open-label substudy and were treated with S100/M2000 for 24 weeks.

RESULTS — The mean baseline A1C was 8.8% in the randomized patients. The placebo-subtracted A1C change from baseline was -2.07% (S100/M2000), -1.57% (S100/M1000), -1.30% (M2000), -0.99% (M1000), and -0.83% (S100) ($P < 0.001$ for comparisons versus placebo and for coadministration versus respective monotherapies). The proportion of patients achieving an A1C <7% and <6.5% was 66 and 44%, respectively, in the S100/M2000 group ($P < 0.001$ vs. S100 or M2000). For the open-label cohort ($n = 117$; baseline A1C 11.2%) treated with S100/M2000, the within-group mean A1C change from baseline was -2.9% . The incidence of hypoglycemia was low (0.5–2.2%) across active treatment groups and not significantly different from that in the placebo group (0.6%). The incidence of gastrointestinal adverse experiences was similar for coadministration therapies compared with their respective metformin monotherapy.

CONCLUSIONS — The initial combination of sitagliptin and metformin provided substantial and additive glycemic improvement and was generally well tolerated in patients with type 2 diabetes.

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