



Dear Doctor:

Thank you for your interest in the enclosed reprint, "Safety and Efficacy of Sitagliptin in Patients with Type 2 Diabetes and Chronic Renal Insufficiency," by J.C.N. Chan, R. Scott, J.C. Arjona Ferreira, et al, as published in the online version of *Diabetes, Obesity and Metabolism*, on June 1, 2008. The objective of the study was to assess the safety of sitagliptin in patients with type 2 diabetes and moderate renal insufficiency (creatinine clearance [CrCl] ≥ 30 to < 50 mL/min) or severe renal insufficiency (CrCl < 30 mL/min including patients with end-stage renal disease [ESRD] on dialysis). The efficacy of sitagliptin in this patient population was also assessed.

The Prescribing Information for JANUVIA™ (sitagliptin) tablets includes a description of the results after 12 weeks of the study described in this reprint. The 54-week results reported in this reprint are not described in the Prescribing Information. As noted in the Prescribing Information, after 12 weeks of therapy a small increase in serum creatinine was reported in patients with moderate renal insufficiency treated with JANUVIA relative to those on placebo.

JANUVIA 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 or angioedema.

No dosage adjustment is required for patients with mild renal insufficiency (CrCl ≥ 50 mL/min, approximately corresponding to serum creatinine levels of ≤ 1.7 mg/dL in men and ≤ 1.5 mg/dL in women).

For patients with 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 JANUVIA 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 ESRD requiring hemodialysis or peritoneal dialysis, the dose of JANUVIA is 25 mg once daily.

Because there is a need for a dose adjustment, assessment of renal function is recommended before initiation of JANUVIA and periodically thereafter.

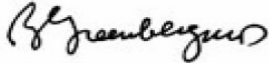
As is typical with other antihyperglycemic agents used in combination with a sulfonylurea, when JANUVIA was used in combination with a sulfonylurea, a class of medications known to cause hypoglycemia, the incidence of hypoglycemia was increased over that of placebo. Therefore, a lower dose of sulfonylurea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

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with JANUVIA™ (sitagliptin), such as 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 reported, regardless of investigator assessment of causality, in $\geq 5\%$ of patients treated with JANUVIA as monotherapy and in combination therapy and more commonly than in patients treated with placebo, were upper respiratory tract infection, nasopharyngitis, and headache.

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.

Sincerely,



Bram Greenberg, MD, FAAP
Executive Director, Medical Services

Enclosure: Prescribing Information for JANUVIA

[Click to view Study Abstract](#)

Safety and Efficacy of Sitagliptin in Patients with Type 2 Diabetes and Chronic Renal Insufficiency

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KEYWORDS

chronic kidney disease • DPP-4 inhibitor • MK-0431 • type 2 diabetes

OBJECTIVE: To assess the safety of sitagliptin in patients with type 2 diabetes and moderate [creatinine clearance (CrCl) ≥ 30 to < 50 ml/min] or severe renal insufficiency [CrCl < 30 ml/min including patients with end-stage renal disease (ESRD) on dialysis]. The efficacy of sitagliptin in this patient population was also assessed.

METHODS: In a 54-week, randomized, double-blind, parallel-group study, patients with baseline glycosylated haemoglobin A_{1c} (HbA_{1c}) values of 6.5–10% were allocated (2:1) to sitagliptin (for 54 weeks) or the sequence of placebo (for 12 weeks) followed by active treatment with glipizide (for 42 weeks). To achieve plasma concentrations similar to those observed in patients with normal renal function treated with 100 mg sitagliptin once daily, patients with moderate renal insufficiency were allocated to receive sitagliptin 50 mg once daily and patients with severe renal insufficiency to receive 25 mg once daily. Glipizide treatment was initiated at 2.5 or 5 mg/day and uptitrated to a maximum of 20 mg/day.

RESULTS: Patients (N = 91) with a mean baseline HbA_{1c} value of 7.7% (range: 6.2–10.3%) were randomized to sitagliptin (n = 65) or placebo (n = 26). After 12 weeks, the mean change [95% confidence interval (CI)] from baseline in HbA_{1c} was -0.6% ($-0.8, -0.4$) in the sitagliptin group compared with -0.2% ($-0.4, 0.1$) in the placebo group [between-group difference (95% CI) = -0.4% ($-0.7, -0.1$)]. At 54 weeks, patients continuously treated with sitagliptin had a mean change (95% CI) from baseline in HbA_{1c} of -0.7% ($-0.9, -0.4$). The overall incidence of adverse experiences was generally similar between groups. Between-group differences in incidences of specific clinical adverse experiences were generally small; however, the proportion of patients for whom hypoglycaemia was reported was lower in the sitagliptin group (4.6%) compared with the placebo/glipizide group (23.1%). Consistent with the high mortality risk in this patient population, there were six deaths during this 54-week study [5 of 65 patients (7.7%) in the sitagliptin group and 1 of 26 patients (3.8%) in the placebo/glipizide group]; no death was considered by the investigator to be drug related. The overall incidences of drug-related and serious adverse experiences and discontinuations because of adverse experiences were generally similar between groups.

CONCLUSIONS: In this study, sitagliptin was generally well tolerated and provided effective glycaemic control in patients with type 2 diabetes and moderate to severe renal insufficiency, including patients with ESRD on dialysis.