

Cimetidine	400 mg	850 mg	Metformin	1.40	1.61
Carbonic anhydrase inhibitors may cause metabolic acidosis [See Warnings and Precautions (5.1) and Drug Interactions (7).]					
Topiramate	100 mg [†]	500 mg [†]	Metformin	1.25 [†]	1.17

* All doses administered as single dose unless otherwise specified

† AUC is reported as AUC_{0-∞} unless otherwise specified

‡ GLUMETZA (metformin HCl extended-release tablets) 500 mg

§ Ratio of arithmetic means

† Steady state 100 mg Topiramate every 12 hr + metformin HCl 500 mg every 12 hr. AUC = AUC_{0-12hr}

13 NONCLINICAL TOXICOLOGY

• 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

JANUMET XR

No animal studies have been conducted with the combined products in JANUMET XR to evaluate carcinogenesis, mutagenesis or impairment of fertility. The following data are based on the findings in studies with sitagliptin and metformin individually.

Sitagliptin

A two-year carcinogenicity study was conducted in male and female rats given oral doses of sitagliptin of 50, 150, and 500 mg/kg/day. There was an increased incidence of combined liver adenoma/carcinoma in males and females and of liver carcinoma in females at 500 mg/kg. This dose results in exposures approximately 60 times the human exposure at the maximum recommended daily adult human dose (MRHD) of 100 mg/day based on AUC comparisons. Liver tumors were not observed at 150 mg/kg, approximately 20 times the human exposure at the MRHD. A two-year carcinogenicity study was conducted in male and female mice given oral doses of sitagliptin of 50, 125, 250, and 500 mg/kg/day. There was no increase in the incidence of tumors in any organ up to 500 mg/kg, approximately 70 times human exposure at the MRHD. Sitagliptin was not mutagenic or clastogenic with or without metabolic activation in the Ames bacterial mutagenicity assay, a Chinese hamster ovary (CHO) chromosome aberration assay, an *in vitro* cytogenetics assay in CHO, an *in vitro* rat hepatocyte DNA alkaline elution assay, and an *in vivo* micronucleus assay.

In rat fertility studies with oral gavage doses of 125, 250, and 1000 mg/kg, males were treated for 4 weeks prior to mating, during mating, up to scheduled termination (approximately 8 weeks total), and females were treated 2 weeks prior to mating through gestation day 7. No adverse effect on fertility was observed at 125 mg/kg (approximately 12 times human exposure at the MRHD of 100 mg/day based on AUC comparisons). At higher doses, nondose-related increased resorptions in females were observed (approximately 25 and 100 times human exposure at the MRHD based on AUC comparison).

Metformin

Long-term carcinogenicity studies have been performed in Sprague Dawley rats at doses of 150, 300, and 450 mg/kg/day in males and 150, 450, 900, and 1200 mg/kg/day in females. These doses are approximately 2, 4, and 8 times in males, and 3, 7, 12, and 16 times in females of the maximum recommended human daily dose of 2000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female rats. A carcinogenicity study was also performed in Tg.AC transgenic mice at doses up to 2000 mg applied dermally. No evidence of carcinogenicity was observed in male or female mice.

Genotoxicity assessments in the Ames test, gene mutation test (mouse lymphoma cells), chromosomal aberrations test (human lymphocytes) and *in vivo* mouse micronucleus tests were negative. Fertility of male or female rats was not affected by metformin when administered at doses up to 600 mg/kg/day, which is approximately 3 times the maximum recommended human daily dose based on body surface area comparisons.

14 CLINICAL STUDIES

The coadministration of sitagliptin and metformin immediate-release has been studied in patients with type 2 diabetes inadequately controlled on diet and exercise and in combination with other antidiabetic medications.

There have been no clinical efficacy or safety studies conducted with JANUMET XR to characterize its effect on hemoglobin A1c (A1C) reduction. Bioequivalence of JANUMET XR tablets with coadministered

sitagliptin and extended-release metformin tablets has been demonstrated for all tablet strengths [see *Clinical Pharmacology* (12.3)].

- **Metformin Extended-Release Compared to Metformin Immediate-Release in Patients with Type 2 Diabetes**

In a multicenter, randomized, double-blind, active-controlled, dose-ranging, parallel group trial extended-release metformin HCl 1500 mg once daily, extended-release metformin HCl 1500 mg per day in divided doses (500 mg in the morning and 1000 mg in the evening), and extended-release metformin HCl 2000 mg once daily were compared to immediate-release metformin HCl 1500 mg per day in divided doses (500 mg in the morning and 1000 mg in the evening). This trial enrolled patients (n = 338) who were newly diagnosed with diabetes, patients treated only with diet and exercise, patients treated with a single anti-diabetic medication (sulfonylureas, alpha-glucosidase inhibitors, thiazolidinediones, or meglitinides), and patients (n = 368) receiving metformin HCl up to 1500 mg/day plus a sulfonylurea at a dose equal to or less than one-half the maximum dose. Patients who were enrolled on monotherapy or combination antidiabetic therapy underwent a 6-week washout. Patients randomized to extended-release metformin HCl began titration from 1000 mg/day up to their assigned treatment dose over 3 weeks. Patients randomized to immediate-release metformin HCl initiated 500 mg twice daily for 1 week followed by 500 mg with breakfast and 1000 mg with dinner for the second week. The 3-week treatment period was followed by an additional 21-week period at the randomized dose. For HbA1c and fasting plasma glucose, each of the extended-release metformin regimens was at least as effective as immediate-release metformin. Additionally, once daily dosing of extended-release metformin was as effective as twice daily dosing of the immediate-release metformin formulation.

- **Sitagliptin and Metformin Immediate-Release Coadministration in Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise**

A total of 1091 patients with type 2 diabetes and inadequate glycemic control on diet and exercise participated in a 24-week, randomized, double-blind, placebo-controlled factorial study designed to assess the efficacy of sitagliptin and metformin immediate-release coadministration. Patients on an antihyperglycemic agent (N=541) underwent a diet, exercise, and drug washout period of up to 12 weeks duration. After the washout period, patients with inadequate glycemic control (A1C 7.5% to 11%) were randomized after completing a 2-week single-blind placebo run-in period. Patients not on antihyperglycemic agents at study entry (N=550) with inadequate glycemic control (A1C 7.5% to 11%) immediately entered the 2-week single-blind placebo run-in period and then were randomized. Approximately equal numbers of patients were randomized to receive placebo, 100 mg of sitagliptin once daily, 500 mg or 1000 mg of metformin HCl immediate-release twice daily, or 50 mg of sitagliptin twice daily in combination with 500 mg or 1000 mg of metformin HCl immediate-release twice daily. Patients who failed to meet specific glycemic goals during the study were treated with glyburide (glibenclamide) rescue.

Sitagliptin and metformin immediate-release coadministration provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo, to metformin immediate-release alone, and to sitagliptin alone (Table 9, Figure 1). For patients not on an antihyperglycemic agent at study entry, mean reductions from baseline in A1C were: sitagliptin 100 mg once daily, -1.1%; metformin HCl immediate-release 500 mg bid, -1.1%; metformin HCl immediate-release 1000 mg bid, -1.2%; sitagliptin 50 mg bid with metformin HCl immediate-release 500 mg bid, -1.6%; sitagliptin 50 mg bid with metformin HCl immediate-release 1000 mg bid, -1.9%; and for patients receiving placebo, -0.2%. Lipid effects were generally neutral. The decrease in body weight in the groups given sitagliptin in combination with metformin immediate-release was similar to that in the groups given metformin alone or placebo.

Table 9: Glycemic Parameters at Final Visit (24-Week Study) for Sitagliptin and Metformin Immediate-Release, Alone and in Combination in Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise*

	Placebo	Sitagliptin 100 mg once daily	Metformin HCl Immediate- Release 500 mg twice daily	Metformin HCl Immediate- Release 1000 mg twice daily	Sitagliptin 50 mg bid + Metformin HCl Immediate- Release 500 mg twice daily	Sitagliptin 50 mg bid + Metformin HCl Immediate- Release 1000 mg twice daily
A1C (%)	N = 165	N = 175	N = 178	N = 177	N = 183	N = 178
Baseline (mean)	8.7	8.9	8.9	8.7	8.8	8.8
Change from baseline (adjusted mean [†])	0.2	-0.7	-0.8	-1.1	-1.4	-1.9
Difference from placebo (adjusted mean [†]) (95% CI)		-0.8 [‡] (-1.1, -0.6)	-1.0 [‡] (-1.2, -0.8)	-1.3 [‡] (-1.5, -1.1)	-1.6 [‡] (-1.8, -1.3)	-2.1 [‡] (-2.3, -1.8)
Patients (%) achieving A1C <7%	15 (9%)	35 (20%)	41 (23%)	68 (38%)	79 (43%)	118 (66%)
% Patients receiving rescue medication	32	21	17	12	8	2
FPG (mg/dL)	N = 169	N = 178	N = 179	N = 179	N = 183	N = 180
Baseline (mean)	196	201	205	197	204	197
Change from baseline (adjusted mean [†])	6	-17	-27	-29	-47	-64
Difference from placebo (adjusted mean [†]) (95% CI)		-23 [‡] (-33, -14)	-33 [‡] (-43, -24)	-35 [‡] (-45, -26)	-53 [‡] (-62, -43)	-70 [‡] (-79, -60)
2-hour PPG (mg/dL)	N = 129	N = 136	N = 141	N = 138	N = 147	N = 152
Baseline (mean)	277	285	293	283	292	287
Change from baseline (adjusted mean [†])	0	-52	-53	-78	-93	-117
Difference from placebo (adjusted mean [†]) (95% CI)		-52 [‡] (-67, -37)	-54 [‡] (-69, -39)	-78 [‡] (-93, -63)	-93 [‡] (-107, -78)	-117 [‡] (-131, -102)

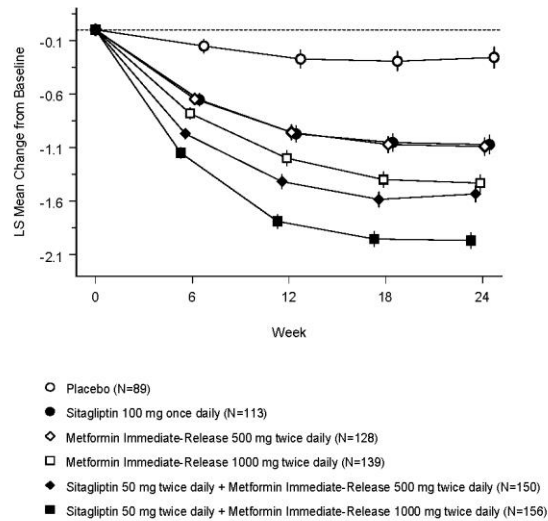
* Intent-to-treat population using last observation on study prior to glyburide (glibenclamide) rescue therapy.

[†] Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.

[‡] p<0.001 compared to placebo.

26.

Figure 1: Mean Change from Baseline for A1C (%) over 24 Weeks with Sitagliptin and Metformin Immediate-Release, Alone and in Combination in Patients with Type 2 Diabetes Inadequately Controlled with Diet and Exercise*



* The Completers Population: least squares means adjusted for prior antihyperglycemic therapy and baseline value.

Initial combination therapy or maintenance of combination therapy should be individualized and are left to the discretion of the health care provider.

• **Sitagliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on Metformin Immediate-Release Alone**

A total of 701 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin in combination with metformin immediate-release. Patients already on metformin HCl immediate-release (N=431) at a dose of at least 1500 mg per day were randomized after completing a 2-week, single-blind placebo run-in period. Patients on metformin immediate-release and another antihyperglycemic agent (N=229) and patients not on any antihyperglycemic agents (off therapy for at least 8 weeks, N=41) were randomized after a run-in period of approximately 10 weeks on metformin HCl immediate-release (at a dose of at least 1500 mg per day) in monotherapy. Patients were randomized to the addition of either 100 mg of sitagliptin or placebo, administered once daily. Patients who failed to meet specific glycemic goals during the studies were treated with pioglitazone rescue.

In combination with metformin immediate-release, sitagliptin provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo with metformin immediate-release (Table 10). Rescue glycemic therapy was used in 5% of patients treated with sitagliptin 100 mg and 14% of patients treated with placebo. A similar decrease in body weight was observed for both treatment groups.

Table 10: Glycemic Parameters at Final Visit (24-Week Study) of Sitagliptin as Add-on Combination Therapy with Metformin Immediate-Release*

	Sitagliptin 100 mg once daily + Metformin Immediate-Release	Placebo + Metformin Immediate-Release
A1C (%)	N = 453	N = 224
Baseline (mean)	8.0	8.0
Change from baseline (adjusted mean [†])	-0.7	-0.0
Difference from placebo + metformin immediate-release (adjusted mean [†]) (95% CI)	-0.7 [‡] (-0.8, -0.5)	

Patients (%) achieving A1C <7%	213 (47%)	41 (18%)
FPG (mg/dL)	N = 454	N = 226
Baseline (mean)	170	174
Change from baseline (adjusted mean [†])	-17	9
Difference from placebo + metformin immediate-release (adjusted mean [†]) (95% CI)	-25 [‡] (-31, -20)	
2-hour PPG (mg/dL)	N = 387	N = 182
Baseline (mean)	275	272
Change from baseline (adjusted mean [†])	-62	-11
Difference from placebo + metformin immediate-release (adjusted mean [†]) (95% CI)	-51 [‡] (-61, -41)	

* Intent-to-treat population using last observation on study prior to pioglitazone rescue therapy.

[†] Least squares means adjusted for prior antihyperglycemic therapy and baseline value.

[‡] p<0.001 compared to placebo + metformin.

- Sitagliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on the Combination of Metformin Immediate-Release and Glimepiride**

A total of 441 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin in combination with glimepiride, with or without metformin immediate-release. Patients entered a run-in treatment period on glimepiride (≥ 4 mg per day) alone or glimepiride in combination with metformin HCl immediate-release (≥ 1500 mg per day). After a dose-titration and dose-stable run-in period of up to 16 weeks and a 2-week placebo run-in period, patients with inadequate glycemic control (A1C 7.5% to 10.5%) were randomized to the addition of either 100 mg of sitagliptin or placebo, administered once daily. Patients who failed to meet specific glycemic goals during the studies were treated with pioglitazone rescue.

Patients receiving sitagliptin with metformin immediate-release and glimepiride had significant improvements in A1C and FPG compared to patients receiving placebo with metformin immediate-release and glimepiride (Table 11), with mean reductions from baseline relative to placebo in A1C of -0.9% and in FPG of -21 mg/dL. Rescue therapy was used in 8% of patients treated with add-on sitagliptin 100 mg and 29% of patients treated with add-on placebo. The patients treated with add-on sitagliptin had a mean increase in body weight of 1.1 kg vs. add-on placebo (+0.4 kg vs. -0.7 kg). In addition, add-on sitagliptin resulted in an increased rate of hypoglycemia compared to add-on placebo. [See *Warnings and Precautions* (5.6); *Adverse Reactions* (6.1).]

Table 11: Glycemic Parameters at Final Visit (24-Week Study) for Sitagliptin in Combination with Metformin Immediate-Release and Glimepiride*

	Sitagliptin 100 mg + Metformin Immediate-Release and Glimepiride	Placebo + Metformin Immediate-Release and Glimepiride
A1C (%)	N = 115	N = 105
Baseline (mean)	8.3	8.3
Change from baseline (adjusted mean [†])	-0.6	0.3
Difference from placebo (adjusted mean [†]) (95% CI)	-0.9 [‡] (-1.1, -0.7)	
Patients (%) achieving A1C <7%	26 (23%)	1 (1%)
FPG (mg/dL)	N = 115	N = 109
Baseline (mean)	179	179
Change from baseline (adjusted mean [†])	-8	13
Difference from placebo (adjusted mean [†]) (95% CI)	-21 [‡] (-32, -10)	

* Intent-to-treat population using last observation on study prior to pioglitazone rescue therapy.

[†] Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.

[‡] p<0.001 compared to placebo.

Sitagliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on the Combination of Metformin Immediate-Release and Rosiglitazone

A total of 278 patients with type 2 diabetes participated in a 54-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin in combination with metformin immediate-release and rosiglitazone. Patients on dual therapy with metformin HCl immediate-release ≥ 1500 mg/day and rosiglitazone ≥ 4 mg/day or with metformin HCl immediate-release ≥ 1500 mg/day and pioglitazone ≥ 30 mg/day (switched to rosiglitazone ≥ 4 mg/day) entered a dose-stable run-in period of 6 weeks. Patients on other dual therapy were switched to metformin HCl immediate-release ≥ 1500 mg/day and rosiglitazone ≥ 4 mg/day in a dose titration/stabilization run-in period of up to 20 weeks in duration. After the run-in period, patients with inadequate glycemic control (A1C 7.5% to 11%) were randomized 2:1 to the addition of either 100 mg of sitagliptin or placebo, administered once daily. Patients who failed to meet specific glycemic goals during the studies were treated with glipizide (or other sulfonylurea) rescue. The primary time point for evaluation of glycemic parameters was Week 18.

In combination with metformin immediate-release and rosiglitazone, sitagliptin provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo with metformin immediate-release and rosiglitazone (Table 12) at Week 18. At Week 54, mean reduction in A1C was -1.0% for patients treated with sitagliptin and -0.3% for patients treated with placebo in an analysis based on the intent-to-treat population. Rescue therapy was used in 18% of patients treated with sitagliptin 100 mg and 40% of patients treated with placebo. There was no significant difference between sitagliptin and placebo in body weight change.

Table 12: Glycemic Parameters at Week 18 for Sitagliptin in Add-on Combination Therapy with Metformin Immediate-Release and Rosiglitazone*

	Week 18	
	Sitagliptin 100 mg + Metformin Immediate-Release + Rosiglitazone	Placebo + Metformin Immediate-Release + Rosiglitazone
A1C (%)	N = 176	N = 93
Baseline (mean)	8.8	8.7
Change from baseline (adjusted mean [†])	-1.0	-0.4
Difference from placebo + rosiglitazone + metformin immediate-release (adjusted mean [†]) (95% CI)	-0.7 [‡] (-0.9, -0.4)	
Patients (%) achieving A1C <7%	39 (22%)	9 (10%)
FBG (mg/dL)	N = 179	N = 94
Baseline (mean)	181	182
Change from baseline (adjusted mean [†])	-30	-11
Difference from placebo + rosiglitazone + metformin immediate-release (adjusted mean [†]) (95% CI)	-18 [‡] (-26, -10)	
2-hour PPG (mg/dL)	N = 152	N = 80
Baseline (mean)	256	248
Change from baseline (adjusted mean [†])	-59	-21
Difference from placebo + rosiglitazone + metformin immediate-release (adjusted mean [†]) (95% CI)	-39 [‡] (-51, -26)	

* Intent-to-treat population using last observation on study prior to glipizide (or other sulfonylurea) rescue therapy.

[†] Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.

[‡] p<0.001 compared to placebo + metformin + rosiglitazone.

Sitagliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on the Combination of Metformin Immediate-Release and Insulin

A total of 641 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin as add-on to insulin therapy. Approximately 75% of patients were also taking metformin immediate-release. Patients entered a 2-week, single-blind run-in treatment period on pre-mixed, long-acting, or intermediate-acting insulin, with or without metformin HCl immediate-release (≥ 1500 mg per day). Patients using short-acting insulins were excluded unless the short-acting insulin was administered as part of a pre-mixed insulin. After the run-in period, patients with inadequate glycemic control (A1C 7.5% to 11%) were randomized to the addition of either 100 mg of sitagliptin (N=229) or placebo (N=233), administered once daily. Patients were on a stable dose of insulin prior to enrollment with no changes in insulin dose permitted during the run-in period. Patients who failed to meet specific glycemic goals during the double-blind treatment period were to have uptitration of the background insulin dose as rescue therapy.

Among patients also receiving metformin immediate-release, the median daily insulin (pre-mixed, intermediate or long acting) dose at baseline was 40 units in the sitagliptin-treated patients and 42 units in the placebo-treated patients. The median change from baseline in daily dose of insulin was zero for both groups at the end of the study. Patients receiving sitagliptin with metformin immediate-release and insulin

had significant improvements in A1C, FPG and 2-hour PPG compared to patients receiving placebo with metformin immediate-release and insulin (Table 13). The adjusted mean change from baseline in body weight was -0.3 kg in patients receiving sitagliptin with metformin immediate-release and insulin and -0.2 kg in patients receiving placebo with metformin immediate-release and insulin. There was an increased rate of hypoglycemia in patients treated with sitagliptin. [See *Warnings and Precautions (5.6); Adverse Reactions (6.1).*]

Table 13: Glycemic Parameters at Final Visit (24-Week Study) for Sitagliptin as Add-on Combination Therapy with Metformin Immediate-Release and Insulin*

	Sitagliptin 100 mg + Metformin Immediate- Release + Insulin	Placebo + Metformin Immediate- Release + Insulin
A1C (%)	N = 223	N = 229
Baseline (mean)	8.7	8.6
Change from baseline (adjusted mean ^{†,‡})	-0.7	-0.1
Difference from placebo (adjusted mean [†]) (95% CI)	-0.5 [§] (-0.7, -0.4)	
Patients (%) achieving A1C <7%	32 (14%)	12 (5%)
FPG (mg/dL)	N = 225	N = 229
Baseline (mean)	173	176
Change from baseline (adjusted mean [†])	-22	-4
Difference from placebo (adjusted mean [†]) (95% CI)	-18 [§] (-28, -8.4)	
2-hour PPG (mg/dL)	N = 182	N = 189
Baseline (mean)	281	281
Change from baseline (adjusted mean [†])	-39	1
Difference from placebo (adjusted mean [†]) (95% CI)	-40 [§] (-53, -28)	

* Intent-to-treat population using last observation on study prior to rescue therapy.

[†] Least squares means adjusted for insulin use at the screening visit, type of insulin used at the screening visit (pre-mixed vs. non pre-mixed [intermediate- or long-acting]), and baseline value.

[‡] Treatment by insulin stratum interaction was not significant (p>0.10).

[§] p<0.001 compared to placebo.

Maintenance of Sitagliptin During Initiation and Titration of Insulin Glargine

A total of 746 patients with type 2 diabetes (mean baseline HbA1C 8.8%, disease duration 10.8 years) participated in a 30-week, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of continuing sitagliptin during the initiation and uptitration of insulin glargine. Patients who were on a stable dose of metformin HCl (≥ 1500 mg/day) in combination with a DPP-4 inhibitor and/or sulfonylurea but with inadequate glycemic control (A1C 7.5% to 11%) were enrolled in the study. Those on metformin and sitagliptin (100 mg/day) directly entered the double-blind treatment period; those on another DPP-4 inhibitor and/or on a sulfonylurea entered a 4-8 week run-in period in which they were maintained on metformin and switched to sitagliptin (100 mg); other DPP-4 inhibitors and sulfonylureas were discontinued. At randomization patients were randomized either to continue sitagliptin or to discontinue sitagliptin and switch to a matching placebo. On the day of randomization, insulin glargine was initiated at a dose of 10 units subcutaneously in the evening. Patients were instructed to uptitrate their insulin dose in the evening based on fasting blood glucose measurements to achieve a target of 72-100 mg/dL.

At 30 weeks, the mean reduction in A1C was greater in the sitagliptin group than in the placebo group (Table 14). At the end of the trial, 27.3% of patients in the sitagliptin group and 27.3% in the placebo group had a fasting plasma glucose (FPG) in the target range; there was no significant difference in insulin dose between arms.

27.

Table 14: Change from Baseline in A1C and FPG at Week 30 in the Maintenance of Sitagliptin During Initiation and Titration of Insulin Glargine Study

	Sitagliptin 100 mg +Metformin + Insulin Glargine	Placebo +Metformin + Insulin Glargine
A1C (%)	N = 373[†]	N = 370[†]
Baseline (mean)	8.8	8.8
Week 30 (mean)	6.9	7.3
Change from baseline (adjusted mean)*	-1.9	-1.4
Difference from placebo (adjusted mean) (95% CI)*	-0.4 (-0.6, -0.3) [‡]	
Patients (%) with A1C <7%	202 (54.2%)	131 (35.4%)
FPG (mg/dL)	N = 373[†]	N = 370[†]
Baseline (mean)	199	201
Week 30 (mean)	118	123
Change from baseline (adjusted mean)*	-81	-76

* Analysis of Covariance including all post-baseline data regardless of rescue or treatment discontinuation. Model estimates calculated using multiple imputation to model washout of the treatment effect using placebo data for all subjects having missing Week 30 data.

[†] N is the number of randomized and treated patients.

[‡] p<0.001 compared to placebo.

- **Sitagliptin Add-on Therapy vs. Glipizide Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on Metformin Immediate-Release**

The efficacy of sitagliptin was evaluated in a 52-week, double-blind, glipizide-controlled noninferiority trial in patients with type 2 diabetes. Patients not on treatment or on other antihyperglycemic agents entered a run-in treatment period of up to 12 weeks duration with metformin HCl immediate-release monotherapy (dose of ≥ 1500 mg per day) which included washout of medications other than metformin immediate-release, if applicable. After the run-in period, those with inadequate glycemic control (A1C 6.5% to 10%) were randomized 1:1 to the addition of sitagliptin 100 mg once daily or glipizide for 52 weeks. Patients receiving glipizide were given an initial dosage of 5 mg/day and then electively titrated over the next 18 weeks to a maximum dosage of 20 mg/day as needed to optimize glycemic control. Thereafter, the glipizide dose was to be kept constant, except for down-titration to prevent hypoglycemia. The mean dose of glipizide after the titration period was 10 mg.

After 52 weeks, sitagliptin and glipizide had similar mean reductions from baseline in A1C in the intent-to-treat analysis (Table 15). These results were consistent with the per protocol analysis (Figure 2). A conclusion in favor of the non-inferiority of sitagliptin to glipizide may be limited to patients with baseline A1C comparable to those included in the study (over 70% of patients had baseline A1C <8% and over 90% had A1C <9%).

Table 15: Glycemic Parameters in a 52-Week Study Comparing Sitagliptin to Glipizide as Add-On Therapy in Patients Inadequately Controlled on Metformin Immediate-Release (Intent-to-Treat Population) *

	Sitagliptin 100 mg + Metformin Immediate-Release	Glipizide + Metformin Immediate-Release
A1C (%)	N = 576	N = 559
Baseline (mean)	7.7	7.6
Change from baseline (adjusted mean [†])	-0.5	-0.6
FPG (mg/dL)	N = 583	N = 568
Baseline (mean)	166	164
Change from baseline (adjusted mean [†])	-8	-8

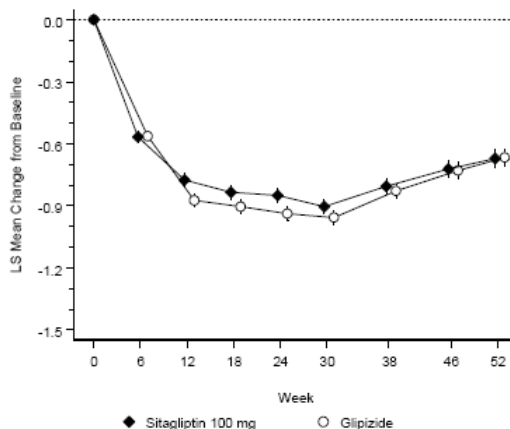
* The intent-to-treat analysis used the patients' last observation in the study prior to discontinuation.

[†] Least squares means adjusted for prior antihyperglycemic therapy status and baseline A1C value.

28.

Figure 2: Mean Change from Baseline for A1C (%) Over 52 Weeks in a Study Comparing Sitagliptin to Glipizide as Add-On Therapy in Patients Inadequately Controlled on Metformin Immediate-Release (Per Protocol Population) *

29.



* The per protocol population (mean baseline A1C of 7.5%) included patients without major protocol violations who had observations at baseline and at Week 52.

30.

The incidence of hypoglycemia in the sitagliptin group (4.9%) was significantly ($p < 0.001$) lower than that in the glipizide group (32.0%). Patients treated with sitagliptin exhibited a significant mean decrease from baseline in body weight compared to a significant weight gain in patients administered glipizide (-1.5 kg vs. +1.1 kg).

16 HOW SUPPLIED/STORAGE AND HANDLING

Tablets supplied as follows:

Contents	Description	How Supplied	NDC
50 mg sitagliptin and 500 mg metformin HCl extended-release	light blue, bi-convex oval, film-coated tablets with "78" debossed on one side	unit-of-use bottles of 60	NDC 0006-0078-61
		unit-of-use bottles of 180	NDC 0006-0078-62
		bulk bottles of 1000	NDC 0006-0078-82
		unit-of-use bottles of 60	NDC 0006-0080-61

50 mg sitagliptin and 1000 mg metformin HCl extended-release	light green, bi-convex oval, film-coated tablets with "80" debossed on one side	unit-of-use bottles of 180	NDC 0006-0080-62
		bulk bottles of 1000	NDC 0006-0080-82
100 mg sitagliptin and 1000 mg metformin HCl extended-release	blue, bi-convex oval, film-coated tablets with "81" debossed on one side	unit-of-use bottles of 30	NDC 0006-0081-31
		unit-of-use bottles of 90	NDC 0006-0081-54
		bulk bottles of 1000	NDC 0006-0081-82

Store at 20-25°C (68-77°F), excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.] Store in a dry place with cap tightly closed. When container is subdivided, dispense into a USP tightly closed, moisture-resistant container.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Lactic Acidosis

Explain the risks of lactic acidosis, its symptoms, and conditions that predispose to its development. Advise patients to discontinue JANUMET XR immediately and to promptly notify their healthcare provider if unexplained hyperventilation, myalgias, malaise, unusual somnolence or other nonspecific symptoms occur. Counsel patients against excessive alcohol intake and inform patients about the importance of regular testing of renal function while receiving JANUMET XR. Instruct patients to inform their doctor that they are taking JANUMET XR prior to any surgical or radiological procedure, as temporary discontinuation may be required [see *Warnings and Precautions (5.1)*].

Pancreatitis

Inform patients that acute pancreatitis has been reported during postmarketing use of JANUMET XR. Inform patients that persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Instruct patients to promptly discontinue JANUMET XR and contact their physician if persistent severe abdominal pain occurs [see *Warnings and Precautions (5.2)*].

Heart Failure

Inform patients of the signs and symptoms of heart failure. Before initiating JANUMET XR, ask patients about a history of heart failure or other risk factors for heart failure including moderate to severe renal impairment. Instruct patients to contact their health care provider as soon as possible if they experience symptoms of heart failure, including increasing shortness of breath, rapid increase in weight or swelling of the feet [see *Warnings and Precautions (5.3)*].

Vitamin B₁₂ Deficiency

Inform patients about the importance of regular monitoring of hematological parameters while receiving JANUMET XR [see *Warnings and Precautions (5.5)*].

Hypoglycemia

Inform patients that the incidence of hypoglycemia is increased when sitagliptin with or without metformin is added to an insulin secretagogue (e.g., sulfonylurea) or insulin therapy. Explain to patients receiving JANUMET XR in combination with these medications the risks of hypoglycemia, its symptoms and treatment and conditions that predispose to its development [see *Warnings and Precautions (5.6)*].

Hypersensitivity Reactions

Inform patients that allergic reactions have been reported during postmarketing use of sitagliptin, one of the components of JANUMET XR. If symptoms of allergic reactions (including rash, hives, and swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing) occur, patients must stop taking JANUMET XR and seek medical advice promptly.

Severe and Disabling Arthralgia

Inform patients that severe and disabling joint pain may occur with this class of drugs. The time to onset of symptoms can range from one day to years. Instruct patients to seek medical advice if severe joint pain occurs [see *Warnings and Precautions (5.8)*].

Bullous Pemphigoid

Inform patients that bullous pemphigoid may occur with this class of drugs. Instruct patients to seek medical advice if blisters or erosions occur [see *Warnings and Precautions (5.9)*].

Administration Instructions

Inform patients that the tablets must be swallowed whole and never split, crushed or chewed.

Incompletely Dissolved Tablets in Feces

Inform patients that incompletely dissolved JANUMET XR tablets may be eliminated in the feces. Tell patients that, if they repeatedly see tablets in feces, they should report this finding to their health care provider. Assess adequacy of glycemic control if a patient reports repeatedly observing tablets in feces.

Females of Reproductive Age:

Inform females that treatment with JANUMET XR may result in ovulation in some premenopausal anovulatory women which may lead to unintended pregnancy [see *Use in Specific Populations (8.3)*].

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