Mechanism of Action

JANUMET® tablets contain two oral antihyperglycemic drugs used in the management of type 2 diabetes: sitagliptin and metformin hydrochloride.

Sitagliptin

Sitagliptin is an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme. It is available in JANUMET® tablets in the form of sitagliptin phosphate monohydrate. Sitagliptin potently and selectively inhibits DPP-4 in vitro and in vivo, with a therapeutic selectivity for the closely-related enzymes DPP-8 or DPP-9 at therapeutic concentrations.

Metformin hydrochloride

Metformin hydrochloride (N,N-dimethylbiguanide dihydrochloride) is not a sulfonylurea and does not produce hypoglycemia in either patients with type 2 diabetes or in normal subjects. Metformin is a biguanide. Metformin is a white to off-white crystalline compound with a molecular formula of C4H11N5•HCl and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68. The structural formula is:

\[
\text{H}_2\text{N} - \text{CH} = \text{CH} - \text{CO} \quad \text{NH} - \text{CH}_2 - \text{CO} \quad \text{NH} - \text{CH}_2 - \text{CO} \quad \text{OH} \quad \text{H}_2\text{O}
\]

THERAPEUTIC CLASS

JANUMET® (sitagliptin/metformin HCl) combines two antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: sitagliptin phosphate, a dipeptidyl peptidase 4 (DPP-4) inhibitor, and metformin hydrochloride, a member of the biguanide class.

Mechanism of Action

Sitagliptin phosphate is an orally-active, potent, and highly selective inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme. DPP-4 is a membrane-bound dipeptidyl peptidase of the peptidase family associated with the extracellular domain of cell surface proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin phosphate monohydrate is described chemically as 7-[[3 trifluorophenyl]butyl]-5,6,7,8- tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-f]fumarate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, red iron oxide, and black iron oxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

JANUMET® tablets contain two oral antihyperglycemic drugs used in the management of type 2 diabetes: sitagliptin phosphate and metformin hydrochloride, a member of the biguanide class.

Sitagliptin phosphate

Sitagliptin phosphate is a member of a class of oral antihyperglycemic agents called dipeptidyl peptidase 4 (DPP-4) inhibitors, which improve glycemic control in patients with type 2 diabetes by enhancing the levels of active incretin hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the small intestine in response to ingestion of food. GLP-1 increases insulin release and decreases glucagon levels in a glucose-dependent manner. In patients with type 2 diabetes with hyperglycemia, these changes in insulin and glucagon levels lead to lower hemoglobin A1c (HbA1c), hepatic glucose output, and postprandial glucose concentrations. The glucose dependent mechanism of sitagliptin is distinct from the mechanism of sulfonylureas, which increases insulin secretion even when glucose levels are low, can cause hypoglycemia, and is often used in combination with thiazolidinediones in patients with type 2 diabetes.

Sitagliptin is a potent and highly selective inhibitor of the enzyme DPP-4 and does not inhibit the closely-related enzymes DPP-8 or DPP-9 at therapeutic concentrations.

Metformin hydrochloride

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes. The primary mechanism of action of metformin is suppression of hepatic glucose production and suppression of glucagon secretion by GLP-1 are not observed. For both GLP-1 and GIP, stimulation of insulin release is enhanced as glucose rises above normal concentrations.

Further, GLP-1 does not impair the normal glucagon response to hypoglycemia. The activity of GLP-1 and GIP is limited by the DPP-4 enzyme, which rapidly hydrolyzes the incretins during their systemic circulation.

JANUMET® tablets combine the glucose-dependent mechanism of sitagliptin with the glucose-dependent mechanism of metformin.

Pharmacokinetics

The results of a definitive bioequivalence study in healthy subjects demonstrated that the JANUMET® (sitagliptin/metformin hydrochloride) 50 mg/500 mg and 25 mg/1000 mg combination tablets were bioequivalent to the individual components, sitagliptin phosphate (JANUVIA™) and metformin hydrochloride as individual tablets.

Absorption

Sitagliptin phosphate

The absolute bioavailability of sitagliptin is approximately 87%. Co-administration of a high-fat meal delays or reduces the rate and extent of sitagliptin absorption.

Metformin hydrochloride

The absolute bioavailability of a metformin hydrochloride 500 mg tablet given under fasting conditions is approximately 50-60%. Studies using single oral doses of metformin hydrochloride tablets 50 mg to 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality at higher doses (greater than 1500 mg) and that sitagliptin can be administered without regard to food.

Distribution

Sitagliptin phosphate

The mean volume of distribution at steady state following a single 100-mg intravenous dose of sitagliptin to healthy subjects is approximately 198 liters. The fraction of sitagliptin reversibly bound to plasma proteins is low (38%).

Metformin hydrochloride

The mean volume of distribution (V/F) of metformin following single oral doses of metformin hydrochloride tablets 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin is approximately 65% bound at therapeutic concentrations.

Following a [\(^{14}\)C]sitagliptin oral dose, approximately 16% of the radioactivity was excreted as unchanged drug in the urine and 8% was excreted as metabolites in the feces. Following oral administration, approximately 87% of the administered radioactivity was eliminated in feces (13%) or urine (87%) within one week of dosing. The apparent terminal \(t_{1/2}\) following a 100-mg oral dose of sitagliptin was 10 hours, and the plasma elimination half-life was 2.6 hours. The apparent terminal \(t_{1/2}\) following oral administration of sitagliptin to healthy volunteers was approximately 1 hour.

Elimination

Sitagliptin phosphate

Following administration of an oral [\(^{14}\)C]sitagliptin dose to healthy subjects, approximately 100% of the radioactivity was recovered in the urine and/or feces (87% within one week in the urine). In clinical trials, the mean plasma elimination half-life of sitagliptin is approximately 1 hour.

Six metabolites were detected at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin. In vitro studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin was CYP2C8, with minor involvement of CYP1A2 and CYP2C9.

Metformin hydrochloride

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion.

Mechanism of Action

Type 2 Diabetes

The pharmacokinetics of sitagliptin in patients with type 2 diabetes are generally similar to those in healthy subjects.

Characteristics in Patients

Type 2 Diabetes

In the presence of normal renal function, there are no differences between single- or multiple-dose pharmacokinetics of metformin in patients with type 2 diabetes and normal subjects, nor is there any accumulation of metformin in either group at usual clinical doses.

Renal Insufficiency

JANUMET® tablets should not be used in patients with renal insufficiency (see CONTRAINDICATIONS).

JANUMET® tablets demonstrated a 2-fold increase in the plasma AUC of sitagliptin was observed in patients with moderate renal insufficiency, and an approximately 4-fold increase was observed in patients with severe renal insufficiency, and in patients with ESRD on hemodialysis, as compared to normal healthy control subjects.

Metformin hydrochloride

Pharmacodynamics

JANUMET® tablets combine two oral antihyperglycemic drugs used in the management of type 2 diabetes: sitagliptin phosphate and metformin hydrochloride, a member of the biguanide class.
In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance.

Hepatic Insufficiency

Sitagliptin phosphate

In patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), mean AUC and Cmax of sitagliptin were elevated by 21% and 22%, respectively, compared to healthy matched controls following administration of a single 100-mg dose of sitagliptin phosphate. These differences were not considered to be clinically meaningful.

There is no clinical experience in patients with severe hepatic insufficiency (Child-Pugh score >9). However, because sitagliptin is primarily eliminated, severe hepatic insufficiency is not expected to impact the pharmacokinetics of sitagliptin.

Metformin hydrochloride

No pharmacokinetic studies of metformin have been conducted in patients with hepatic insufficiency.

Gender

Sitagliptin phosphate

Gender had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase II data, including subjects of white, Hispanic, black, Asian, and other racial groups.

Metformin hydrochloride

No pharmacokinetic data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and Cmax is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function (see GLUCOPHAGE® prescribing information: CLINICAL PHARMACOLOGY. Sitagliptin phosphate).

Elderly

Sitagliptin phosphate

Age did not have a clinically meaningful impact on the pharmacokinetics of sitagliptin based on a population pharmacokinetic analysis of Phase I and Phase II data. Elderly subjects (65 to 80 years) and approximately 15% higher plasma concentrations of sitagliptin compared to younger subjects.

Metformin hydrochloride

Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and Cmax is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function (see GLUCOPHAGE® prescribing information: CLINICAL PHARMACOLOGY. Sitagliptin phosphate).

Pediatric

No studies with JANUMET have been performed in pediatric patients.

Race

Sitagliptin phosphate

Race had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase II data, including subjects of white, Hispanic, black, Asian, and other racial groups.

Metformin hydrochloride

No pharmacokinetic data from controlled pharmacokinetic studies of metformin in healthy subjects with normal blood pressure.

Body Mass Index

Sitagliptin phosphate

Body mass index (BMI) had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase II data.

Pharmacokinetics

Sitagliptin phosphate

In patients with type 2 diabetes, administration of single oral doses of sitagliptin leads to inhibition of DPP-4 enzyme activity for a 24-hour period, resulting in a 2- to 3-fold increase in active GLP-1 concentrations, increased plasma levels of insulin and C-peptide, decreased glucagon concentrations, reduced fasting glucose, and reduced glucose excursion following an oral glucose load or a meal.

Sitagliptin is eliminated predominantly in the urine via glucuronidation, following a 2- to 3-fold increase in active GLP-1 concentrations, as compared to placebo. Reductions have been observed in subjects with normal blood pressure.

In patients with type 2 diabetes, the antihypertensive effect of sitagliptin was generally well tolerated. In these patients, sitagliptin had a modest blood pressure lowering effect; 100 mg per day of sitagliptin reduced 24-hour mean ambulatory systolic blood pressure by approximately 2 mm Hg, as compared to placebo. Reductions have been observed in patients with normal blood pressure. These differences are not considered to be clinically meaningful.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No animal studies have been conducted with the combined products in JANUMET to evaluate carcinogenesis, mutagenesis or impairment of fertility. The following data are based on the components of JANUMET: Sitagliptin phosphate

In a long-term carcinogenicity study 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 was approximately 50 times the human exposure at the maximum recommended daily human dose (MRHD) of 100 mg/day based on AUC comparisons. No sex-related effect was observed at 150 mg/kg/day, the maximum 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 combined tumor types up to 250 mg/kg/day and no increase in male mice and female mice at the maximum recommended daily human dose (MRHD) of 100 mg/day based on AUC comparisons).

Sitagliptin phosphate 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 CHO cell assay, an in vitro mouse lymphoma (L5178Y) microsome assay, and an in vivo micronucleus assay.

In a randomized, placebo-controlled crossover study, 79 healthy subjects were administered a single oral dose of sitagliptin 100 mg, sitagliptin 800 mg (8 times the recommended dose), and placebo on different days with an interval between treatments of approximately 25 and 100 mg/kg/day.

In patients with normal blood pressure, no evidence of a mutagenic potential of metformin in the following in vitro tests: Ames test (S. typhimurium), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the in vivo mouse micronucleus test were also negative; no evidence of the mutagenic potential of metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

There have been no clinical efficacy studies conducted with JANUMET; however, bioequivalence of JANUMET with co-administered sitagliptin and metformin hydrochloride has been demonstrated.

Sitagliptin and Metformin Co-Administration in Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise†

In patients with type 2 diabetes inadequately controlled on diet and exercise participated in a 24-week, randomized, double-blind, placebo-controlled factorial study to evaluate the efficacy and safety of sitagliptin and metformin co-administration (Sitagliptin 50 mg, Metformin 500 mg b.i.d. or placebo, -0.2%; Lipid effects were generally neutral. The decrease in body weight in the groups receiving sitagliptin and metformin co-administration was statistically significant for Sitagliptin and Metformin, Alone and in Combination in Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise†

**Table 1 Glycemic Parameters at Final Visit (24-Week Study) for Sitagliptin and Metformin, Alone and in Combination in Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise†**

**Figure 1:** Mean Change from Baseline for HbA1c, over 24 Weeks with Sitagliptin, Metformin, Alone and in Combination in Patients with Type 2 Diabetes Inadequately Controlled with Diet and Exercise**
Table 2: Glycemic Parameters at Final Visit (24-Week Study) of Sitagliptin in Add-on Combination Therapy with Metformin 1

<table>
<thead>
<tr>
<th>Treatment</th>
<th>HbA1c (%)</th>
<th>FPG (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + Metformin</td>
<td>N = 224</td>
<td>N = 224</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>8.0</td>
<td>281</td>
</tr>
<tr>
<td>N = 453</td>
<td></td>
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<tr>
<td>Placebo + Metformin</td>
<td>N = 224</td>
<td>N = 224</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>8.0</td>
<td>281</td>
</tr>
<tr>
<td>N = 453</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo + Metformin</td>
<td>N = 224</td>
<td>N = 224</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>8.0</td>
<td>281</td>
</tr>
<tr>
<td>N = 453</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Least squares means adjusted for prior antihyperglycemic therapy and baseline value.
2 p<0.001 compared to placebo + metformin.

Table 3: Glycemic Parameters at Final Visit (24-Week Study) for Sitagliptin in Combination with Metformin and Glimepiride

<table>
<thead>
<tr>
<th>Treatment</th>
<th>HbA1c (%)</th>
<th>FPG (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + Metformin + Glimepiride</td>
<td>N = 224</td>
<td>N = 224</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>8.3</td>
<td>281</td>
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<tr>
<td>N = 453</td>
<td></td>
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<tr>
<td>Placebo + Metformin + Glimepiride</td>
<td>N = 224</td>
<td>N = 224</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>8.3</td>
<td>281</td>
</tr>
<tr>
<td>N = 453</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo + Metformin + Glimepiride</td>
<td>N = 224</td>
<td>N = 224</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>8.3</td>
<td>281</td>
</tr>
<tr>
<td>N = 453</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Least squares means adjusted for prior antihyperglycemic therapy and baseline value.
2 p<0.001 compared to placebo + metformin.

Table 4: Glycemic Parameters at Week 18 for Sitagliptin in Add-on Combination Therapy with Metformin and Rosiglitazone

<table>
<thead>
<tr>
<th>Treatment</th>
<th>HbA1c (%)</th>
<th>FPG (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + Metformin</td>
<td>N = 337</td>
<td>N = 337</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>8.7</td>
<td>281</td>
</tr>
<tr>
<td>N = 223</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo + Metformin</td>
<td>N = 337</td>
<td>N = 337</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>8.7</td>
<td>281</td>
</tr>
<tr>
<td>N = 223</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo + Metformin</td>
<td>N = 337</td>
<td>N = 337</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>8.7</td>
<td>281</td>
</tr>
<tr>
<td>N = 223</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Least squares means adjusted for prior antihyperglycemic therapy and baseline value.
2 p<0.01 compared to placebo + metformin.

Table 5: Glycemic Parameters at Final Visit (24-Week Study) for Sitagliptin and Glimepiride in Combination Therapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>HbA1c (%)</th>
<th>FPG (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + Metformin</td>
<td>N = 337</td>
<td>N = 337</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>8.7</td>
<td>281</td>
</tr>
<tr>
<td>N = 223</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo + Metformin</td>
<td>N = 337</td>
<td>N = 337</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>8.7</td>
<td>281</td>
</tr>
<tr>
<td>N = 223</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo + Metformin</td>
<td>N = 337</td>
<td>N = 337</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>8.7</td>
<td>281</td>
</tr>
<tr>
<td>N = 223</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Least squares means adjusted for prior antihyperglycemic therapy and baseline value.
2 p<0.001 compared to placebo + metformin.

Table 6: Glycemic Parameters in a 52-Week Study Comparing Sitagliptin to Glipizide as Add-On Therapy in Patients Inadequately Controlled on Metformin (intent-to-Treat Population)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>HbA1c (%)</th>
<th>FPG (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + Metformin</td>
<td>N = 426</td>
<td>N = 426</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>8.4</td>
<td>281</td>
</tr>
<tr>
<td>N = 291</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo + Metformin</td>
<td>N = 426</td>
<td>N = 426</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>8.4</td>
<td>281</td>
</tr>
<tr>
<td>N = 291</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo + Metformin</td>
<td>N = 426</td>
<td>N = 426</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>8.4</td>
<td>281</td>
</tr>
<tr>
<td>N = 291</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Least squares means adjusted for prior antihyperglycemic therapy and baseline value.
2 p<0.01 compared to placebo + metformin.
Ssitagliptin 100 mg + Metformin

Glipizide + Metformin

HbA₁c (%) N=376 N=559
Mean (±SD) 7.7 (±1.8) 7.8 (±1.4)
Change from baseline (mean±SEM) 0.5 (±0.8) 0.2 (±0.6)
FGP (mg/dL) N=363 N=568
Mean (±SEM) 8.8 (±1.8) 9.1 (±1.9)
Change from baseline (mean±SEM) -0.4 (±0.7) -0.0 (±0.8)

The intent to Treat Analysis used the patients’ last observation in the study prior to discontinuation.

1 Least squares means adjusted for prior antihyperglycemic therapy status and baseline HbA₁c value.

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).

INDICATIONS

JANUMET is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus who are not adequately controlled on metformin or sitagliptin alone, or in patients already being treated with the combination of sitagliptin and metformin.

DOSAGE AND ADMINISTRATION

General:
The advantage of antihyperglycemic therapy with JANUMET should be individualized on the basis of the patient’s current regimen, effectiveness, and tolerability while not exceeding the maximum recommended dose of either component.

JANUMET should generally be administered twice daily with meals, with gradual dose escalation, to reduce the gastrointestinal (GI) side effects associated with metformin.

The starting dose of JANUMET should be based on the patient’s current regimen. JANUMET should be given twice daily with meals. The following doses are available:

- 50 mg sitagliptin/850 mg metformin hydrochloride
- 100 mg sitagliptin/1000 mg metformin hydrochloride
- 150 mg sitagliptin/1125 mg metformin hydrochloride

For patients inadequately controlled on monotherapy:

- For patients inadequately controlled on sitagliptin monotherapy:
  - The usual starting dose of JANUMET should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose). In determining the starting dose of the metformin component, the patient’s level of glycaemic control and current dose (if any) of metformin should be considered. Gradual dose escalation to reduce the gastrointestinal (GI) side effects associated with metformin should be considered. Patients currently on or initiating a sulfonylurea may require lower sulfonylurea doses to reduce the risk of hypoglycemia.
  - For patients inadequately controlled on dual combination therapy of metformin and a PPAR-γ agonist (i.e. thiazolidinediones):
    - The usual starting dose of JANUMET should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose). In determining the starting dose of the metformin component, the patient’s level of glycaemic control and current dose (if any) of metformin should be considered. Gradual dose escalation to reduce the gastrointestinal (GI) side effects associated with metformin should be considered. For patients inadequately controlled on dual combination therapy of metformin and insulin:
    - The usual starting dose of JANUMET should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose). In determining the starting dose of the metformin component, the patient’s level of glycaemic control and current dose (if any) of metformin should be considered. Gradual dose escalation to reduce the gastrointestinal (GI) side effects associated with metformin should be considered. For patients inadequately controlled on dual combination therapy of metformin and insulin:
    - The usual starting dose of JANUMET should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose). In determining the starting dose of the metformin component, the patient’s level of glycaemic control and current dose (if any) of metformin should be considered. Gradual dose escalation to reduce the gastrointestinal (GI) side effects associated with metformin should be considered. For patients inadequately controlled on dual combination therapy of metformin and sulfonylurea:
    - The usual starting dose of JANUMET should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose). In determining the starting dose of the metformin component, the patient’s level of glycaemic control and current dose (if any) of metformin should be considered. Gradual dose escalation to reduce the gastrointestinal (GI) side effects associated with metformin should be considered. For patients inadequately controlled on dual combination therapy of metformin and sulfonylurea:
    - The usual starting dose of JANUMET should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose). In determining the starting dose of the metformin component, the patient’s level of glycaemic control and current dose (if any) of metformin should be considered. Gradual dose escalation to reduce the gastrointestinal (GI) side effects associated with metformin should be considered.
Sitagliptin phosphate such studies have been conducted with the individual components of JANUMET, sitagliptin and metformin. Pharmacokinetic drug interaction studies with JANUMET have not been performed; however, Co-administration of multiple doses of sitagliptin (50 mg b.i.d.) and metformin (1000 mg b.i.d.) based on a careful assessment of renal function. (see PRECAUTIONS). In clinical studies, the safety and effectiveness of sitagliptin in the elderly (≥65 years,) were more commonly seen in older patients (<65 years). Metformin hydrochloride Metformin hydrochloride in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 and 6 times the maximum recommended human daily dose of 2.0 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a lack of fetal toxicity to metformin. NURSING MOTHERS There are no adequate and well-controlled studies in pregnant women with JANUMET or its individual components; therefore, the safety of JANUMET in pregnant women is not known. Juvenile diabetes mellitus has been reported in children. No animal studies have been conducted with the combined products in JANUMET to evaluate embryonic and fetal toxicity. Fetal resorption data are based on findings in studies performed with sitagliptin or metformin individually. Sitagliptin phosphate Sitagliptin was not teratogenic in rats at oral doses up to 250 mg/kg or in rabbits given up to 125 mg/kg during organogenesis (up to 32 and 22 times, respectively, the human exposure based on body surface area comparisons for rats and rabbits). In a single-dose study in type 2 diabetes patients, co-administration of furosemide and nifedipine increased the AUC and Cmax of sitagliptin by 20% and 9%, respectively, and increased the amount excreted in the urine. T max of sitagliptin was not affected. No evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones. Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with a variety of other drugs that utilize these pathways. In Vivo Assessment of Drug Interactions Sitagliptin is a p-glycoprotein substrate, but does not inhibit p-glycoprotein-mediated transport of digoxin. Based on these results, sitagliptin is considered unlikely to cause interactions with other drugs that utilize these pathways. Sitagliptin is not an inhibitor of CYP isozymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6, and is not an inducer of CYP3A4. Sitagliptin phosphate is a p-glycoprotein substrate, but does not inhibit p-glycoprotein-mediated transport of digoxin. Therefore, sitagliptin is considered unlikely to cause interactions with other drugs that utilize these pathways. Sitagliptin is not extensively bound to plasma proteins. Therefore, the propensity of sitagliptin to be displaced by other xenobiotics is low; however, drug-drug interactions may be used by plasma protein binding displacement is very low. Sitagliptin and metformin are generally well tolerated. No studies in lactating animals have been conducted with the combined components of JANUMET. In studies performed with the individual components, both sitagliptin and metformin are generally well tolerated. Metformin is used extensively in patients with chronic renal failure. Therefore, JANUMET should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function (see PRECAUTIONS, Monitoring of Renal Function). Sitagliptin phosphate in clinical controlled trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B12 levels, without clinical manifestations, was observed in approximately 7% of patients treated with metformin. These decreases were not considered clinically important. Sitagliptin and Metformin Sitagliptin and Metformin in combination with metformin at 500 or 1000 mg twice daily, the drug-related adverse reactions were those expected with single-dose studies of metformin or sitagliptin. For the combination therapy, the patient should be closely observed to maintain adequate glycemic control. Sitagliptin phosphate In a single-dose interaction study in type 2 diabetes patients, co-administration of nifedipine and glyburide did not change in any significant manner. Sitagliptin and metformin are generally well tolerated. Sitagliptin is not an inhibitor of CYP3A4-mediated metabolism. Therefore, interactions by co-administered medications: Glyburide: In a single-dose interaction study in type 2 diabetes patients, co-administration of sitagliptin and glyburide did not result in any changes in either sitagliptin or glyburide plasma concentrations. Therefore, it seems unlikely that sitagliptin and glyburide would significantly affect each other’s pharmacokinetics. The combination was well tolerated. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cyclosporine pharmacokinetics. Although such interactions remain theoretical (except for the specific case of warfarin), they are not expected to be clinically meaningful. Other: Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid hormone, antipsychotic drugs (e.g., clozapine), oral Contraceptives, systemic steroids, and paclitaxel. The warfarin-protein binding displacement is very low. The potential for interaction with warfarin is low as sitagliptin is not an inducer of CYP2C9 or CYP3A4. However, sitagliptin is a p-glycoprotein substrate and does not inhibit p-glycoprotein-mediated transport of digoxin. Based on these results, sitagliptin is considered unlikely to cause interactions with other drugs that utilize these pathways. Sitagliptin phosphate in clinical controlled trials of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B12 levels, without clinical manifestations, was observed in approximately 7% of patients treated with metformin. These decreases were not considered clinically important. Sitagliptin and Metformin in combination with metformin at 500 or 1000 mg twice daily, the drug-related adverse reactions were those expected with single-dose studies of metformin or sitagliptin. For the combination therapy, the patient should be closely observed to maintain adequate glycemic control. Sitagliptin phosphate in clinical controlled trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B12 levels, without clinical manifestations, was observed in approximately 7% of patients treated with metformin. These decreases were not considered clinically important. Sitagliptin and Metformin in combination with metformin at 500 or 1000 mg twice daily, the drug-related adverse reactions were those expected with single-dose studies of metformin or sitagliptin. For the combination therapy, the patient should be closely observed to maintain adequate glycemic control. 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Abdominal Pain† 4 (2.3) 6 (3.4) 14 (3.8) 11 (3.0) 9 (3.8) 10 (2.2)
Vomiting 1 (0.6) 0 (0.0) 2 (0.5) 8 (2.1) 2 (0.8) 5 (1.1)
Nausea 2 (1.1) 2 (1.1) 20 (5.5) 18 (4.8) 2 (0.8) 6 (1.3)
Diarrhea 7 (4.0) 5 (2.8) 28 (7.7) 28 (7.5) 6 (2.5) 11 (2.4)

In the placebo-controlled study of sitagliptin 100 mg daily added to ongoing combination treatment with metformin and rosiglitazone, the drug-related adverse reactions reported through the primary time point at Week 18 in ≥1% of patients treated with sitagliptin (N=170) and more commonly than in patients treated with placebo (N=92) were: headache (sitagliptin, 2.4%; placebo, 0.0%), diarrhea (1.8%, 1.1%), nausea (1.2%, 1.1%), hypoglycemia (1.2%, 0.0%), and vomiting (1.2%, 0.0%). Through Week 54, the drug-related adverse reactions reported in ≥1% of patients treated with sitagliptin and more commonly than in patients treated with placebo were: headache (2.4%, 0.0%), hypoglycemia (2.4%, 0.0%), upper respiratory tract infection (1.9%, 0.0%), acute upper respiratory tract infection (1.2%, 1.1%), cough (1.2%, 0.0%), fungal skin infection (1.2%, 0.0%), peripheral edema (1.2%, 0.0%), and vomiting (1.2%, 0.0%).

Table 8 Hypoglycemia and Pre-specified Gastrointestinal Intestinal Adverse Experiences (Regardless of Investigator Assessment of Causality) Reported in Patients Receiving Combination Therapy†

<table>
<thead>
<tr>
<th>Number of Patients (%)</th>
<th>Placebo</th>
<th>Sitagliptin 100 mg and Metformin</th>
<th>Sitagliptin 50 mg and Metformin</th>
<th>Placebo</th>
<th>Sitagliptin 100 mg and Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>N=177</td>
<td>N=175</td>
<td>N=164</td>
<td>N=237</td>
<td>N=237</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>1 (0.6)</td>
<td>2 (1.2)</td>
<td>6 (3.8)</td>
<td>2 (0.8)</td>
<td>6 (1.3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (4.0)</td>
<td>5 (2.8)</td>
<td>28 (7.7)</td>
<td>18 (4.8)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (1.1)</td>
<td>2 (1.1)</td>
<td>20 (5.5)</td>
<td>18 (4.8)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
<td>2 (0.5)</td>
<td>8 (2.1)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Constipation</td>
<td>3 (1.7)</td>
<td>2 (1.1)</td>
<td>28 (7.7)</td>
<td>11 (4.2)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>4 (2.3)</td>
<td>4 (2.3)</td>
<td>14 (3.8)</td>
<td>10 (4.2)</td>
<td>3 (1.3)</td>
</tr>
</tbody>
</table>

In the study of initial therapy, Abdominal Distention was reported in 1 Abdominal Pain. Data are for patients given the lower and higher doses of metformin. Please refer to the Metformin label. Additional adverse reactions have been identified during postmarketing use of JANUMET or sitagliptin have been used alone and/or in combination with other antihyperglycemic agents. 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.

Hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions including Stevens-Johnson syndrome (see CONTRAINDICATIONS and PRECAUTIONS). Hypersensitivity reactions: acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis (see Limitations of Use and PRECAUTIONS); worsening renal function, including acute renal failure (sometimes requiring dialysis); upper respiratory tract infection; nasopharyngitis; constipation; vomiting; headache.

LABORATORY TEST FINDINGS

Sitagliptin phosphate

The incidence of laboratory adverse experiences was similar in patients treated with sitagliptin and metformin (7.6%) compared to patients treated with placebo (6.7%). Across clinical studies, a small increase in white blood cell count (approximately 200 cells/μl) during the first week of sitagliptin therapy was observed. Placebo treatment was associated with a small decrease in white blood cell count (approximately 200 cells/μl). A small increase in leukocytes was observed due to a small increase in neutrophils. This observation was seen in most but not all studies. This change in laboratory parameters is not considered to be clinically relevant. The incidence of laboratory adverse experiences was similar in patients treated with sitagliptin and metformin (7.6%) compared to patients treated with placebo (6.7%). Across clinical studies, a small increase in white blood cell count (approximately 200 cells/μl) during the first week of sitagliptin therapy was observed. Placebo treatment was associated with a small decrease in white blood cell count (approximately 200 cells/μl). A small increase in leukocytes was observed due to a small increase in neutrophils. This observation was seen in most but not all studies. This change in laboratory parameters is not considered to be clinically relevant. Metformin hydrochloride.

In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B12 levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B12 absorption from the B9-intrinsic factor complex, is, however, very rarely associated with anemia and anemia is not always consistent with discontinuation of metformin or Vitamin B12 supplementation (see PRECAUTIONS, Metformin hydrochloride).

OVERDOSAGE

Sitagliptin phosphate

During controlled clinical trials in healthy subjects, single doses of up to 800 mg sitagliptin were generally well tolerated. Minimal increases in QTC, not considered to be clinically relevant, were observed in one study at a dose of 800 mg sitagliptin (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Cardiac Electrophysiology). There is no experience with doses above 800 mg in humans. In Phase I multiple-dose studies, there were no dose-related clinical adverse reactions observed with sitagliptin with doses of up to 400 mg per day for periods of up to 28 days. In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy if required. Sitagliptin is modestly dialyzable. In clinical studies, approximately 13.5% of the dose was removed over a 3- to 4-hour hemodialysis session. Prolonged hemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialyzable by peritoneal dialysis.

Metformin hydrochloride

Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases (see PRECAUTIONS, Metformin hydrochloride). Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdose is suspected.

STORAGE

Store up to 30°C (86°F).

DOSE FORMS AND STRENGTHS

• 50 mg/500 tablets are light pink, capsule-shaped, film-coated tablets with “575” debossed on one side.
• 50 mg/850 tablets are pink, capsule-shaped, film-coated tablets with “515” debossed on one side.
• 50 mg/1000 tablets are red, capsule-shaped, film-coated tablets with “577” debossed on one side.

A-2000's.