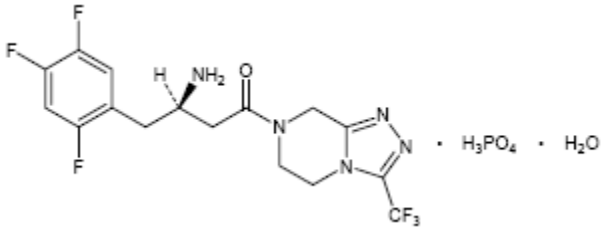
Sitagliptin Phosphate

JANUVIA Tablets contain sitagliptin phosphate, an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme. Sitagliptin phosphate monohydrate is described chemically as 7-[(3*R*)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-*a*]pyrazine phosphate (1:1) monohydrate.

The empirical formula is $C_{16}H_{15}F_6N_5O \cdot H_3PO_4 \cdot H_2O$ and the molecular weight is 523.32. The structural formula is:



Sitagliptin phosphate monohydrate is a white to off-white, crystalline, non-hygroscopic powder. It is soluble in water and N,N-dimethyl formamide; slightly soluble in methanol; very slightly soluble in ethanol, acetone, and acetonitrile; and insoluble in isopropanol and isopropyl acetate.

Each film-coated tablet of JANUVIA contains 32.13, 64.25, or 128.5 mg of sitagliptin phosphate monohydrate, which is equivalent to 25, 50, or 100 mg, respectively, of free base and the following inactive ingredients: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, magnesium stearate, and sodium stearyl fumarate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, red iron oxide, and yellow iron oxide.

Monotherapy and Combination Therapy

JANUVIA is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.]

Important Limitations of Use

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.

Recommended Dosing

The recommended dose of JANUVIA is 100 mg once daily. JANUVIA can be taken with or without food.

Patients with Renal Insufficiency

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

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 end-stage renal disease (ESRD) requiring hemodialysis or peritoneal dialysis, the dose of JANUVIA is 25 mg once daily. JANUVIA may be administered without regard to the timing of hemodialysis.

Because there is a need for dosage adjustment based upon renal function, assessment of renal function is recommended prior to initiation of JANUVIA and periodically thereafter. Creatinine clearance can be estimated from serum creatinine using the Cockcroft-Gault formula.

Concomitant Use with a Sulfonylurea

When JANUVIA is used in combination with a sulfonylurea, a lower dose of sulfonylurea may be required to reduce the risk of hypoglycemia.

SIDE EFFECTS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In controlled clinical studies as monotherapy and combination therapy with metformin or pioglitazone, the overall incidence of adverse reactions, hypoglycemia, and discontinuation of therapy due to clinical adverse reactions with JANUVIA were similar to placebo.

In combination with glimepiride, with or without metformin, the overall incidence of clinical adverse reactions with JANUVIA was higher than with placebo, in part related to a higher incidence of hypoglycemia; the incidence of discontinuation due to clinical adverse reactions was similar to placebo.

Hypersensitivity reactions include anaphylaxis, angioedema, rash, urticaria, and exfoliative skin conditions including Stevens-Johnson syndrome.

The most common side effects of JANUVIA include:

- Upper respiratory infection
- Stuffy or runny nose and sore throat
- Headache
- May occasionally cause stomach discomfort and diarrhea

Instructions

Patients should be informed of the potential risks and benefits of JANUVIA and of alternative modes of therapy. Patients should also

be informed about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and A1C testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications. During periods of stress such as fever, trauma, infection, or surgery, medication requirements may change and patients should be advised to seek medical advice promptly.

Patients should be informed that allergic reactions have been reported during post marketing use of JANUVIA. 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 JANUVIA and seek medical advice promptly.

PRECAUTIONS

Use in Patients with Renal Insufficiency

A dosage adjustment is recommended in patients with moderate or severe renal insufficiency and in patients with ESRD requiring hemodialysis or peritoneal dialysis.

Use with Medications Known to Cause Hypoglycemia

As is typical with other anti-hyperglycemic 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.

Hypersensitivity Reactions

There have been post marketing 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.

Use in Specific Populations

Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women; this drug should be used during pregnancy only if clearly needed.

Sitagliptin is secreted in the milk of lactating rats at a milk to plasma ratio of 4:1. It is not known whether sitagliptin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when JANUVIA is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of JANUVIA in pediatric patients under 18 years of age have not been established.

Geriatric Use

No overall differences in safety or effectiveness were observed between subjects 65 years and over and younger subjects. While this and other reported clinical experience have not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in the elderly, and it may be useful to assess renal function in these patients prior to initiating dosing and periodically thereafter.

Overdose

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 as dictated by the patient's clinical status.

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.

Pharmacokinetics

The pharmacokinetics of sitagliptin has been extensively characterized in healthy subjects and patients with type 2 diabetes. After oral administration of a 100 mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median T max) occurring 1 to 4 hours post dose. Plasma AUC of sitagliptin increased in a dose-proportional manner. Following a single oral 100 mg dose to healthy volunteers, mean plasma AUC of sitagliptin was 8.52 μM•hr, Cmax was 950 nM, and apparent terminal half-life (t1/2) was 12.4 hours. Plasma AUC of sitagliptin increased approximately 14% following 100 mg doses at steady-state compared to the first dose. The intra-subject and inter-subject coefficients of variation for sitagliptin AUC were small (5.8% and 15.1%). The pharmacokinetics of sitagliptin was generally similar in healthy subjects and in patients with type 2 diabetes.

Absorption

The absolute bioavailability of sitagliptin is approximately 87%. Because co-administration of a high-fat meal with JANUVIA had no effect on the pharmacokinetics, JANUVIA may be administered with or without food.

Hepatic Insufficiency

No dosage adjustment for JANUVIA is necessary for patients with mild or moderate hepatic insufficiency.

Drug Interactions

Sitagliptin is not extensively bound to plasma proteins. Therefore, the propensity of sitagliptin to be involved in clinically meaningful drug–drug interactions mediated by plasma protein binding displacement is very low.

Effects of Sitagliptin on Other Drugs

In clinical studies, as described below, sitagliptin did not meaningfully alter the pharmacokinetics of metformin, glyburide, simvastatin, rosiglitazone, warfarin, or oral contraceptives.

Digoxin: Sitagliptin had a minimal effect on the pharmacokinetics of digoxin. Following administration of 0.25 mg digoxin concomitantly with 100 mg of JANUVIA daily for 10 days, the plasma AUC of digoxin was increased by 11%, and the plasma Cmax by 18%.

Metformin: Co-administration of multiple twice-daily doses of sitagliptin with metformin, an OCT substrate, did not meaningfully alter the pharmacokinetics of metformin in patients with type 2 diabetes. Therefore, sitagliptin is not an inhibitor of OCT-mediated transport.

Sulfonylureas: Single-dose pharmacokinetics of glyburide, a CYP2C9 substrate, was not meaningfully altered in subjects receiving multiple doses of sitagliptin. Clinically meaningful interactions would not be expected with other sulfonylureas (e.g., glipizide, tolbutamide, and glimepiride) which, like glyburide, are primarily eliminated by CYP2C9.

Simvastatin: Single-dose pharmacokinetics of simvastatin, a CYP3A4 substrate, was not meaningfully altered in subjects receiving multiple

daily doses of sitagliptin. Therefore, sitagliptin is not an inhibitor of CYP3A4-mediated metabolism.

Thiazolidinediones: Single-dose pharmacokinetics of rosiglitazone, was not meaningfully altered in subjects receiving multiple daily doses of sitagliptin, indicating that JANUVIA is not an inhibitor of CYP2C8-mediated metabolism.

Warfarin: Multiple daily doses of sitagliptin did not meaningfully alter the pharmacokinetics, as assessed by measurement of S (-) or R (+) warfarin enantiomers, or pharmacodynamics (as assessed by measurement of prothrombin INR) of a single dose of warfarin. Because S(-) warfarin is primarily metabolized by CYP2C9, these data also support the conclusion that sitagliptin is not a CYP2C9 inhibitor.

Oral Contraceptives: Co-administration with sitagliptin did not meaningfully alter the steady-state pharmacokinetics of norethindrone or ethinyl estradiol.

Cyclosporine: A study was conducted to assess the effect of cyclosporine, a potent inhibitor of p-glycoprotein, on the pharmacokinetics of sitagliptin. Co-administration of a single 100 mg oral dose of JANUVIA and a single 600 mg oral dose of cyclosporine increased the AUC and Cmax of sitagliptin by approximately 29% and 68%, respectively. These modest changes in sitagliptin pharmacokinetics were not considered to be clinically meaningful. The renal clearance of sitagliptin was also not meaningfully altered. Therefore, meaningful interactions would not be expected with other p-glycoprotein inhibitors.

Glycemic Parameters at Final Visit (24-Week Study) for JANUVIA in Combination with Glimepiride, with or without Metformin*

A1C (%)	JANUVIA 100 mg+ Glimepiride N = 102	Placebo +Glimepiride N = 103	JANUVIA 100 mg+ Glimepiride + Metformin	Placebo+ Glimepiride+ Metformin N = 105

			N = 115	
Baseline (mean)	8.4	8.5	8.3	8.3
Change from baseline (adjusted mean†)	-0.3	0.3	-0.6	0.3
Difference from placebo (adjusted mean†) (95% CI)	-0.6‡ (-0.8, -0.3)		-0.9‡ (-1.1, -0.7)	
Patients (%) achieving A1C <7%	11 (11%)	9 (9%)	26 (23%)	1 (1%)
FPG (mg/dL)	**N = 104**	**N = 104**	**N = 115**	**N = 109**
Baseline (mean)	183	185	179	179
Change from baseline (adjusted mean†)	-1	18	-8	13
Difference from placebo (adjusted mean†)	-19§ (-32, -7)		-21‡ (-32, -10)	

(95% CI)

* 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.
§$p < 0.01$ compared to placebo.

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