



PHARMACY CORNER

E. P. C. M. S.

Sitagliptin (Januvia™): A New Mechanism for Treating Type 2 Diabetes Mellitus

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Sitagliptin (Januvia™) is a new medication recently approved (October 17th, 2006) by the FDA for the treatment of Type 2 Diabetes Mellitus (T2DM). It is the first agent in a new class of diabetes medications called dipeptidyl-peptidase-IV (DPP-4) inhibitors.^{1,2} Sitagliptin is approved for use in type 2 diabetics as an adjunct to diet and exercise or in combination with metformin or peroxisome proliferator-activated receptor gamma (PPAR- α) agonists (e.g. thiazolidinediones).^{2,3} Over 2,700 diabetic patients have been treated with sitagliptin for a minimum of 12 weeks and results have demonstrated reductions in HbA_{1c} (A1C) concentrations, as well as fasting and postprandial glucose levels.^{3,4} This new class of agents provides healthcare providers with an additional modality for achieving glycemic control in type 2 diabetics.

PHARMACOLOGY

Sitagliptin is believed to improve glycemic control in type 2 diabetics by acting as a DPP-4 inhibitor.^{2,4} DPP-4 is an enzyme that is responsible for the degradation of incretin hormones (i.e. glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), which are released by the gut in response to meals. Normally, incretin hormones are rapidly degraded by DPP-4. However, sitagliptin increases levels of endogenous incretins by inhibiting this enzyme.²

Incretins help to maintain glucose homeostasis by facilitating the response of the pancreas and liver to glucose fluctuations.⁴ GLP-1 and GIP increase the release of insulin from beta cells in response to elevations in blood glucose levels after a glucose load or meal. It is important to note that sitagliptin works in a glucose-dependent manner and blood glucose concentrations < 90 mg/dL do not allow for increased insulin secretion by GLP-1.^{4,5} Sitagliptin did not result in hypoglycemia in studies in healthy subjects.² In addition to its effects on pancreatic beta cells, GLP-1 inhibits alpha cell production of glucagon resulting in decreased hepatic glucose production, as well as the slowing of gastric emptying.^{2,4}

PHARMACODYNAMICS AND PHARMACOKINETICS

Studies have shown that the administration of sitagliptin results in inhibition of DPP-4 activity for a 24 hour period.² It is administered orally with an absolute bioavailability of 87%.² Furthermore, the extent of absorption does not appear to be affected by food and peak plasma concentrations are reached 1-4 hours after administration.⁴ Sitagliptin has a volume of dis-

tribution of 198 liters and plasma protein binding is limited to 38%.^{2,4} Hepatic metabolism of sitagliptin by CYP3A4 and CYP2C8 is limited with approximately 16% excreted as metabolites. It is estimated that 79% of the dose is excreted unchanged in the urine, primarily through active tubular secretion. The terminal half-life of sitagliptin is about 12.4 hours.⁴

INDICATIONS, DOSING AND ADMINISTRATION

Sitagliptin is approved for use as monotherapy in addition to diet and exercise or in combination with metformin or PPAR- α agonists if monotherapy is not sufficient.² The recommended dose for monotherapy or combination therapy is 100 mg by mouth daily taken with or without food. Because of its renal elimination, dose adjustments of sitagliptin are necessary in patients with renal dysfunction (see Table 1).^{2,4} A combination product of sitagliptin and metformin was approved by the FDA in April 2007. This product is marketed as Janumet™ and is available in the following strengths: 500 mg metformin/50 mg sitagliptin and 1000 mg metformin/50 mg sitagliptin. Janumet™ is approved for use as an adjunct to diet and exercise in patients with type 2 diabetes and in those not adequately controlled on metformin or sitagliptin alone. It should be administered orally twice daily with meals.⁴

SAFETY

Sitagliptin is generally well tolerated. In clinical trials, the rate of adverse drug reactions (ADR) were not statistically different from placebo. The most commonly reported ADR's are upper respiratory infection, nasopharyngitis, and headache. Rates of hypoglycemia were similar to placebo.² It should be noted that DPP-4 is also involved in the metabolism of other peptides (e.g. neuropeptide Y, growth hormone-releasing hormone, vasoactive intestinal polypeptide) as well as in the activation of T-cells. However, long-term safety data is limited and the consequences of the effects on non-incretin hormones remain to be seen.⁵ Interactions with other drugs that are metabolized by the cytochrome P-450 system are unlikely since sitagliptin is not an inhibitor or inducer of the CYP isoenzymes.² However, co-administration of sitagliptin with digoxin did have a minimal effect on the pharmacokinetics of digoxin. An 11% increase in the area under the curve (AUC) and an 18% increase in the average peak drug concentration (C_{max}) of digoxin was observed after administration of 100 mg of sitagliptin for 10 days. It is not necessary to make any dose adjustments to digoxin in patients

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receiving concomitant sitagliptin, but appropriate monitoring is recommended.²

CLINICAL TRIALS

A number of studies on the use of sitagliptin in patients with diabetes have been conducted. Raz and colleagues⁶ evaluated the use of sitagliptin compared to placebo in 521 patients with Type 2 diabetes. Adult subjects with A1C 7-10% (mean 8.1%) were randomized to either sitagliptin 100 or 200 mg or placebo for 18 weeks. Reduction of A1C was significant in the sitagliptin groups compared to placebo (placebo-subtracted A1C reduction: -0.60% in 100 mg group and -.48% in 200 mg group, $p \leq 0.001$). Fasting plasma glucose values were also reduced to a greater extent in the sitagliptin treatment groups.

Charbonnel et al.⁷ evaluated the efficacy and safety of sitagliptin in combination with metformin in 701 patients with Type 2 diabetes. In this study, patients completed a diet/exercise and metformin titration/stabilization period before being randomized to receive either metformin (≥ 1500 mg/day) in combination with sitagliptin (100 mg/day) or placebo for a period of 24 weeks. The average baseline A1C for this population was 8.0%. At the end of the study, treatment with sitagliptin led to a significant reduction in A1C compared to placebo (-0.65%, $p < 0.001$). In addition to significant reductions in fasting plasma glucose and 2-hour postprandial glucose, significantly more patients in the sitagliptin group achieved an A1C $< 7\%$ relative to placebo (47% vs. 18.3%, $p < 0.001$). Combination therapy with sitagliptin and metformin was well tolerated and incidence of adverse drug reactions including hypoglycemia were similar in both groups.

The combination of sitagliptin and pioglitazone was evaluated by Rosenstock and colleagues⁸ in 353 subjects with A1C 7-10%. Patients who were not previously receiving pioglitazone entered an 8-14 week pioglitazone dose titrating and stabilization period before being randomized to receive pioglitazone (30 or 45 mg/day) in combination with either sitagliptin 100 mg or placebo for a period of 24 weeks. Combination therapy significantly reduced A1C compared to placebo (-0.7%, $p < 0.001$). Significant reductions in fasting plasma glucose as well as the proportion of patients achieving target A1C $< 7\%$ also occurred in the sitagliptin group. There was no increased risk of hypoglycemia with the combination of sitagliptin as compared to placebo, and the incidence of other adverse drug reactions were similar between treatment groups.

SUMMARY

The approval of sitagliptin has provided clinicians with an additional mechanism of action that can be used to help achieve glycemic control in type 2 diabetics. This is especially important since almost two-thirds of these patients do not achieve the target A1C goal of $< 7\%$.⁹ Because sitagliptin is new to the market and there are no long-term outcome studies at this time, the exact role of this agent in the treatment of diabetes still remains to be seen. At this point in time, combination studies with sitagliptin and sulfonylureas are ongoing. Furthermore, post-marketing evaluation of sitagliptin as add-on therapy to insulin is expected to begin in the near future.¹⁰ Despite the lack

of long-term safety and efficacy data, the approval of sitagliptin provides clinicians and patients with an orally administered, once-daily treatment option to help patients achieve treatment goals.

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Table 1 ^{2,4,10}

Indication	Type 2 DM in addition to diet and exercise or in combination with metformin or PPAR- α agonists (thiazolidinediones)				
Dosing	CrCl = 50 mL/min: 100 mg daily CrCl = 30 to < 50 mL/min: 50 mg daily CrCl < 30 mL/min or on hemodialysis*: 25 mg daily				
Administration	Orally, with or without food				
Pharmacokinetics	PB 38%	Vd 198L	Metabolism Limited metabolism via CYP 3A4, 2C8	Elimination 87% (79% unchanged) in urine; 13% feces	T_{1/2} 12.4 h
Precautions	Patients w/ moderate-severe renal impairment or end-stage renal disease Safety and efficacy have not been established in patients < 18 years of age Pregnancy (Category B); Excretion in breast milk unknown Safety and efficacy have not been established in patients with severe hepatic impairment (Child-Pugh Score > 9)				
Contraindications	Hypersensitivity to sitagliptin; Use in patients with diabetic ketoacidosis or in patients with Type I DM				
Interactions	Co-administration of digoxin (11% \uparrow AUC; 18% \uparrow c _{max}) – no dosing adjustment recommended				
Adverse Reactions	Upper respiratory tract infections, headache, nasopharyngitis				

* Sitagliptin may be administered independently of hemodialysis
PB= protein binding; V= volume of distribution; T_{1/2}= elimination half-life

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