

# Januvia™ (sitagliptin phosphate monohydrate)

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## Mechanism of Action<sup>1,2</sup>

Januvia™ is a selective dipeptidyl peptidase IV (DPP-4) inhibitor which works by enhancing the incretin system in the body, thus decreasing blood glucose. When the body senses hyperglycemia, incretins stimulate the pancreas to release insulin and signal the liver to stop glucose production. The DPP-4 enzyme rapidly hydrolyzes the incretin hormones to inactive products; therefore, inhibiting the enzyme increases the active levels of incretin hormones in the body, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP).

## Pharmacodynamics/Pharmacokinetics<sup>3</sup>

- Absorption: Rapid
- Distribution: 198 L
- Protein binding: 38%
- Metabolism: Not extensively metabolized; minor metabolism via CYP3A4 and 2C8 to metabolites (inactive) suggested by in vitro studies
- Bioavailability: 87%
- Half-life elimination: 12 hours
- Time to peak, plasma: 1-4 hours
- Excretion: Urine 87% (79% as unchanged drug, 16% as metabolites); feces 13%

## Indications<sup>2</sup>

Januvia is indicated in combination with metformin in adult patients with type 2 diabetes mellitus to improve glycemic control when diet and exercise, plus metformin do not provide adequate glycemic control.

## Contraindications<sup>3</sup>

- Hypersensitivity to sitagliptin or any other component of the formulation
- Type 1 diabetes mellitus (insulin dependent, IDDM)
- Diabetic ketoacidosis

## Warnings and Precautions<sup>3</sup>

### Disease-related concerns

- Renal impairment: Use with caution in patients with moderate-to-severe renal dysfunction and end-stage renal disease (ESRD) requiring hemodialysis or peritoneal dialysis; dosing adjustment required.

### Concurrent drug therapy issues

- Sulfonylureas: Use caution when used in conjunction with sulfonylureas; risk of hypoglycemia is increased. Monitor blood glucose closely; dosage adjustments of the sulfonylurea may be necessary.

### Special populations

- Pediatrics: Safety and efficacy have not been established in children <18 years of age.

## Use in Pregnancy<sup>2</sup>

Januvia™ is not recommended for use in pregnancy as the safety has not been established.

## Adverse Effects<sup>2,3</sup>

- Central nervous system: Headache (5%)
- Gastrointestinal: Diarrhea (3%)
- Respiratory: Upper respiratory tract infection (6%), nasopharyngitis (5%)

Post marketing and/or case reports: Anaphylaxis, angioedema, exfoliative dermatitis, hypoglycemia (risk increased in conjunction with sulfonylureas), Stevens-Johnson syndrome.

## Supplied<sup>2</sup>

Januvia™ is available as a 100 mg tablet.

## Dosage and Administration<sup>3</sup>

Oral - Adults with Type 2 diabetes: 100 mg once daily with or without food.

### Dosage adjustment in renal impairment:

$Cl_{cr} \geq 30$  to  $< 50$  mL/minute: 50 mg once daily

$S_{cr}$ : Males:  $> 1.7$  to  $\leq 3.0$  mg/dL; Females:  $> 1.5$  to  $\leq 2.5$  mg/dL: 50 mg once daily

$Cl_{cr} < 30$  mL/minute: 25 mg once daily

$S_{cr}$ : Males:  $> 3.0$  mg/dL; Females:  $> 2.5$  mg/dL: 25 mg once daily

End stage renal disease requiring hemodialysis or peritoneal dialysis: 25 mg once daily; administered without regard to timing of hemodialysis.

## Monitoring Parameters<sup>3</sup>

- HbA<sub>1C</sub> and fasting blood glucose
- Renal function prior to initiation and periodically during treatment

## Safety/Efficacy<sup>2,4,5,6,7</sup>

Due to the progressive nature of type 2 diabetes, many patients who have achieved glycemic control with monotherapy will eventually require combination drug therapy, along with diet and exercise, to maintain glycemic control over time. Clinical trials done with Januvia™ have shown consistent safety and efficacy results for this new product. With its distinct mechanism of action, when used in combination with metformin in patients who do not have adequate glycemic control, it has shown to have clinically significant sustainable reductions in patient's hemoglobin A<sub>1C</sub> (HbA<sub>1C</sub>). When compared to other oral antihyperglycemic agents, it has shown to have similar fasting plasma glucose and 2 hour postprandial glucose reductions; however, the advantage is the reductions in HbA<sub>1C</sub> seem to be sustainable. Also, other advantages include: a convenient once daily dosing regimen; it has been well tolerated in studies with a low risk of hypoglycemia; and it has a neutral effect on body weight. Another potential benefit of Januvia™ is that it may improve beta cell function, but further research needs to be done as there is limited evidence in this area.

**Cost** (Prices from McKesson + Professional Fees)  
1 month supply (34 days) - \$120.20

### **Drug Status**

- Approved by Health Canada
- Not currently on the Saskatchewan Drug Formulary

### **References**

- 1) Investigational Medicines for Diabetes: *Sitagliptin (Januvia) and Vildagliptin (Galvus)*. Pharmacist's Letter/Prescriber's Letter 2006;22:220715.
- 2) Product monograph for *Januvia*. Merck Frosst Canada Ltd., Kirkland, QC, December 2007. Retrieved 21JAN2008; Available from: <http://www.merckfrosst.ca>
- 3) Januvia. *Lexi-Drugs* Online. 1978-2008 Lexi-Comp Inc. Retrieved 24JAN2008; cited: <http://online.lexi.com.cyber.usask.ca/cr/online?siteid=293>
- 4) Goldstein BJ, Feinglos MN, Lunceford JK, Johnson J, Williams-Herman DE. Effect of initial combination therapy with Sitagliptin, a dipeptidyl peptidase-4 inhibitor, and Metformin on glycemic control in patients with Type 2 Diabetes. *Diabetes Care*, May 2007: 30, 1979-1897.
- 5) Charbonnel B, Karasik A, Liu J, Wu M, Meininger G. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor Sitagliptin added to ongoing Metformin therapy in patients with Type 2 Diabetes inadequately controlled with Metformin alone. *Diabetes Care*, March 2006: 29, 2638-2643.
- 6) Aschner P, Kipnes M, Lunceford JK, Sanchez M, Mickel C, Williams-Herman DE. Effect of the dipeptidyl peptidase-4 inhibitor Sitagliptin as monotherapy on glycemic control in patients with Type 2 Diabetes. *Diabetes Care*, September 2006: 29, 2632-2637.
- 7) Brazg R, Xu L, Dalla Man C, Cobelli C, Thomas K, Stein PP. Effect of adding sitagliptin, a dipeptidyl peptidase-4 inhibitor, to metformin on 24-h glycemic control and beta-cell function in patients with type 2 diabetes. *Diabetes, Obesity & Metabolism*, March 2007: 9(2), 186-193.