

Sitagliptin (JANUVIA®)

What is sitagliptin?^{1,2,3}

- Sitagliptin is a new class of oral anti-hyperglycemic known as a DPP-4 inhibitor or incretin enhancer for the treatment of Type 2 diabetes mellitus (T2DM). Sitagliptin is dosed at 100mg daily {Cost \$300/3 months, non-formulary SK & NIHB}. It may be taken with or without food {Availability: Canada: 100mg tablets only; USA: 25mg, 50mg and 100mg strengths}
- Sitagliptin inhibits GI mediated dipeptidyl-peptidase-4 (DPP-4) which is responsible for inactivation and degradation of incretin hormones. The enhanced action of incretin stimulates insulin release & decreases glucagon secretion, resulting in lower A1C and lower fasting & postprandial glucose levels. This action enhances the body's response to food while minimizing hypoglycaemia.

How much does sitagliptin improve A1C & glucose levels?^{3,4,5}

- A Cochrane Review²⁰⁰⁸ of 11 studies (12-52 weeks), including over 6000 patients⁶, found sitagliptin reduced A1C levels by an average of 0.7%⁶, with similar efficacy as monotherapy or add-on therapy. {Actual A1C effect will vary e.g. greater if initial A1C higher or in newly diagnosed T2DM. Data describing a more powerful A1C reduction is available for combination use with metformin.}
- Sitagliptin has also shown significant reduction in fasting and postprandial glucose (PPG) levels.

What is the effect of sitagliptin on weight?³

- Sitagliptin is considered to be weight neutral; no clinically significant ↑ or ↓ in weight has been observed.

Does sitagliptin cause hypoglycemia?³

- Hypoglycemia is uncommon with sitagliptin. Mild to moderate hypoglycaemia has occurred when sitagliptin is given with other oral hypoglycemics (esp. sulfonylureas). Severe hypoglycaemia has been reported in only a few patients.

What are other potential adverse effects with sitagliptin?¹

- **Common side effects** include (compared to placebo):
 - Upper respiratory tract infection (4.5-6.3%)
 - Nasopharyngitis (5.2-6.3%)
 - Urinary tract infection (3.2%)
 - Headache (1.1-5.9%)
 - Arthralgias (3%)
 - Other side effects may include sore throat, cough, fatigue, dizziness, edema, nausea, and diarrhea
- **Hypersensitivity** reactions such as anaphylaxis, angioedema, & exfoliative skin conditions (Stevens-Johnson Syndrome) as well as increased liver function tests have been reported rarely. (FDA caution)

As with most new drugs, safety data is limited. There is some potential concern for possible effects on peptides other than incretins (e.g. neuropeptides, cytokines, lymphocytes & chemokines also affected by DPP-4).

What are other potential cautions regarding the use of sitagliptin?^{1,2,3}

- Sitagliptin should **not** be used in patients with:
 - Moderate or severe renal insufficiency (caution) – if used, reduce dose:

CrCl 30-50ml/min – 50mg daily	CrCl <30 ml/min – 25mg daily	Dialysis – 25mg daily
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 - Severe liver dysfunction
 - Patients under 18 years of age
- Sitagliptin is not recommended for use in pregnancy or during lactation due to lack of adequate trials.
- To date, there are no significant drug interactions reported with sitagliptin.
- DPP-4 is expressed in many tissues, including lymphocytes, and as sitagliptin inhibits DPP-4, this has raised concern over its effect on the immune system and inflammatory mediators. Other drugs in this class of agents have demonstrated increased liver function tests, skin reactions (vildagliptin, saxagliptin) and decreased lymphocytes (saxagliptin).

What is the potential role for sitagliptin in patients with Type 2 diabetes?^{2,7,10}

- Sitagliptin is approved for use in Canada as add-on therapy to metformin. {In the U.S., it is approved for use as monotherapy & combination therapy with metformin, pioglitazone, rosiglitazone, glyburide, or glipizide (not with insulin). In Australia sitagliptin is approved for dual therapy if use of metformin or sulfonylurea contraindicated or inadequate in achievement of A1C target.¹¹}
- Clinical studies have shown improvement in beta-cell function, suggesting a potential for preservation of beta-cells.
- **Metformin** is the drug of choice for T2DM due to long term evidence in decreasing morbidity & mortality. Sitagliptin, added to metformin, may be helpful in patients with inadequate glycemic and/or PPG control.

- Sitagliptin is a new agent with the advantages of a new mechanism, a strong PPG lowering effect, weight neutral and a low risk of hypoglycemia. Its disadvantages are a lack of any clinical outcome trials, high cost, non-formulary status and unknown long-term safety. In patients who have not achieved optimal glycemic control on metformin monotherapy, sitagliptin may be considered as one of the possible 2nd drugs which can be added to metformin. In the new ADA Oct 2008 recommendations, sitagliptin is **not** a Tier 1 or Tier 2 agent, but rather rated as a lower **other** therapeutic option.¹²

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6. Richter B, Banderia-Echtler E, Bergerhoff K, Lerch CI. Dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes mellitus. Cochrane Database of Systematic reviews 2008. CD006739.
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