Canadian Agency for Drugs and Technologies in Health

COMMON DRUG REVIEW

# CEDAC FINAL RECOMMENDATION

## SITAGLIPTIN RESUBMISSION
## (Januvia – Merck Frosst Canada Ltd.)
## Indication: Type 2 Diabetes Mellitus

This recommendation supersedes the CEDAC recommendation for this drug and indication dated June 18, 2008.

**Recommendation:**
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that sitagliptin be listed as a third drug added on to metformin and a sulfonylurea for patients with inadequate glycemic control on metformin and a sulfonylurea and for whom insulin is not an option.

**Reasons for the Recommendation:**
1. In one double-blind randomized controlled trial, patients with inadequate glycemic control on a sulfonylurea plus metformin who had sitagliptin added on to therapy, had statistically significantly greater reductions in haemoglobin A1c, fasting plasma glucose and two-hour post-prandial glucose compared with patients who had placebo added on to therapy.

2. At the confidential price submitted, the daily cost of sitagliptin is more than the daily cost of sulfonylureas but similar to or less than the daily cost of rosiglitazone. The confidential price of sitagliptin was used to make the CEDAC recommendation and the manufacturer requested that this information be kept confidential pursuant to the CDR Confidentiality Guidelines.

**Of Note:**
The Committee noted that in patients with an inadequate response on metformin and a sulfonylurea, a CADTH Therapeutic Review Panel has recommended that insulin NPH is the preferred therapy. However, both the Panel and CEDAC also recognized that insulin may not be an option for all patients.

**Background:**
Sitagliptin has a Health Canada indication for:


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- use 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.
- use in combination with metformin and a sulfonylurea in adult patients with type 2 diabetes mellitus to improve glycemic control when diet and exercise, and dual therapy with these agents, do not provide adequate glycemic control.
- use as monotherapy as an adjunct to diet and exercise to improve glycemic. This indication was not the focus of this recommendation.

The Health Canada recommended dose of sitagliptin is 100 mg once daily. Sitagliptin is available as a 100 mg unscored tablet.

**Submission History:**
Sitagliptin was previously reviewed by CEDAC for use 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 and received a recommendation of do not list (see Notice of CEDAC Final Recommendation, June 18, 2008).

The original Common Drug Review (CDR) systematic review of sitagliptin included four double-blind randomized controlled trials (DB RCTs) (Studies P020, P053, P801, and P036) comparing sitagliptin 100 mg daily with placebo, as add-on to metformin therapy in a total of 2,255 adult patients with type 2 diabetes mellitus. One of the four trials (P801) also included an active comparator group (rosiglitazone 8 mg daily as an add-on to metformin); however, the trial was not powered for comparisons between the active treatments. The four studies demonstrated that, compared with placebo, sitagliptin plus metformin provided statistically significant reductions in hemoglobin A1c compared with placebo plus metformin. There were no data on the effect of sitagliptin on clinically important diabetes-related vascular outcomes. The trials conducted were short-term and the long-term safety of sitagliptin was unknown. None of the four studies were conducted in the population requested for reimbursement by the manufacturer, i.e., patients with a contraindication to or intolerant of a sulfonylurea, and its place in therapy relative to less expensive therapies was unclear.

The manufacturer's resubmission is based on a new confidential price and new clinical information.

**Summary of CEDAC Considerations:**
The Committee considered the following information prepared by CDR: a systematic review of RCTs of sitagliptin and a critique of the manufacturer's pharmacoeconomic evaluation. The manufacturer submitted a confidential price for sitagliptin.

***Clinical Trials***
The CDR systematic review included six new DB RCTs.

Three active comparator trials evaluated sitagliptin as add-on therapy in adult patients with type 2 diabetes mellitus and inadequate glycemic control on metformin:
- The Rigby Study was a published, 16-week, open-label RCT that compared sitagliptin


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100 mg daily with rosiglitazone 4 mg daily in 112 patients stabilized on metformin 1,500 mg to 2,250 mg daily.

- The Wysham study was an unpublished (abstract only), 26-week, DB RCT comparing sitagliptin 100 mg daily with pioglitazone 45 mg daily in 331 patients stabilized on metformin (dose not reported).

- Study 056 was an unpublished, 18-week, non-inferiority DB RCT comparing sitagliptin 100 mg daily with saxagliptin 5 mg daily in 801 patients receiving metformin 1,500 mg to 3,000 mg daily.

One placebo-controlled trial evaluated sitagliptin as an add-on therapy in adult patients with type 2 diabetes mellitus uncontrolled on both metformin and rosiglitazone:

- Study P052 was an unpublished (abstract only), manufacturer-sponsored 54-week DB RCT comparing sitagliptin 100 mg with placebo in 278 patients stabilized on metformin (median dose 2,000 mg daily) and rosiglitazone (median dose 8 mg daily).

One placebo-controlled trial evaluated sitagliptin as an add-on therapy in adult patients with type 2 diabetes mellitus and inadequate glycemic control on a sulfonylurea alone or on metformin and a sulfonylurea.

- Study P035 was a published manufacturer-sponsored DB RCT comparing sitagliptin with placebo in 441 patients, some of whom were inadequately controlled on glimepiride alone (stratum one, n = 212) and some of whom were inadequately controlled on glimepiride and metformin (stratum two, n = 229). Only results from stratum two met the inclusion criteria of the CDR systematic review.

One study was a small (N = 24), 12-week RCT that was not considered because of problems with the validity of the data analysis.

Baseline hemoglobin A1c ranged from 7.7% to 8.8% across the trials. A run-in phase was used in P056 and P035, which selected for patients who were compliant with therapy and which may have improved response rates compared with those observed in clinical practice. It was unclear if there was a run-in phase in the Wysham study. The proportion of patients completing the studies was not reported for the Wysham study and it was over 80% for Study 056 and Study P035.

***Outcomes***

The primary outcome in the Rigby Study, Study P056, Study P052, and P035 was the change from baseline in hemoglobin A1c. It is unclear what constitutes a minimum clinically important reduction in hemoglobin A1c. The primary outcome was not stated in the Wysham study.

The Committee discussed other outcomes that were defined a priori in the CDR systematic review protocol including weight change, hypoglycemia, and quality of life. Quality of life was measured using the Impact of Weight on Quality of Life, the Psychological General Well-being, and the European Quality of Life-5 Dimensions (EQ-5D) scales. None of the trials were designed to measure diabetes-related morbidity and mortality.


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### *Results*

#### *Efficacy or Effectiveness*

- In patients inadequately controlled on metformin alone, the reduction from baseline in hemoglobin A1c was similar when sitagliptin was compared with rosiglitazone (-0.4% versus -0.6%, respectively), with pioglitazone (-0.9% versus -1.2%, respectively) and with saxagliptin (-0.6% versus -0.5%, respectively).
- In patients inadequately controlled on metformin and glimepiride, sitagliptin produced a statistically significantly greater reduction in hemoglobin A1c compared with placebo at 24 weeks, mean difference (MD): -0.89% (95%CI: -1.10 to -0.68, P < 0.001).

#### *Harms (Safety and Tolerability)*

- In four of the five studies considered by the Committee, serious adverse events, adverse events, and withdrawals due to adverse events were similar between sitagliptin and comparators. Harms were not reported in the Wysham study.
- There were no episodes of hypoglycemia that required medical or non-medical assistance among patients receiving sitagliptin in any of the new trials.
- The proportion of patients reporting overall hypoglycemia was similar between sitagliptin and saxagliptin in Study 056, but it was greater for sitagliptin compared with placebo in Study P052 (4% versus 1%, respectively) and Study P035 (16% versus 1%, P < 0.001, respectively).
- Statistical analyses of weight changes were not conducted in the active comparator trials; however, the mean weight change was numerically greater for sitagliptin compared with rosiglitazone and for sitagliptin compared with pioglitazone. Differences in weight change compared with saxagliptin were not reported in Study 056. In Study P035, in patients with an inadequate response on metformin and glimepiride, sitagliptin produced a numerically greater increase in weight compared with placebo (0.4 kg versus -0.7 kg).

#### *Cost and Cost-Effectiveness*

The manufacturer submitted a cost-utility analysis comparing sitagliptin with a sulfonylurea or with a thiazolidinedione, when taken in combination with metformin. The Januvia Diabetes Economic Model was used to estimate long-term diabetes-related complications and associated costs. Treatment effects were based on data from Study P801 (which included sitagliptin and rosiglitazone groups) and Study P024 (which included sitagliptin and glipizide groups). Study P024 was not included in the CDR systematic review as glipizide is not available in Canada. The cumulative incidence of diabetes-related complications over a 50-year time horizon was estimated using equations from the United Kingdom Prospective Diabetes Study (UKPDS) 68, and decreases in patients' utilities were applied based on the diabetes-related complications and adverse events (e.g., hypoglycemia, weight gain). The manufacturer reported that sitagliptin plus metformin costs less and is more effective than a thiazolidinedione plus metformin and is associated with an incremental cost per quality-adjusted life-year of $33,682 versus a sulfonylurea plus metformin. CDR found that the cost-effectiveness results became less favourable when model inputs and assumptions varied, and when compared with a sulfonylurea, the incremental cost per quality-adjusted life-year estimates increased in excess of


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$100,000. The manufacturer's results for thiazolidinediones were robust to variation in key model inputs and assumptions.

Based on the confidential price submitted, the daily cost of sitagliptin (100 mg; $[redacted]) is considerably more than the daily cost of a sulfonylurea ($0.04 to $0.75) and alpha-glucosidase inhibitors (50 mg to 100 mg three times daily; $0.78 to $1.08), comparable to the daily cost of generic pioglitazone (15 mg to 45 mg; $1.57 to $3.35), and less than the daily cost of rosiglitazone (4 mg to 8 mg; $2.34 to $3.35). The confidential price of sitagliptin was used to make the CEDAC recommendation and the manufacturer requested that this information be kept confidential pursuant to the CDR Confidentiality Guidelines.

**Other Discussion Points:**

- Therapeutic reviews by CADTH and subsequent recommendations are that in patients inadequately controlled on metformin, sulfonylurea agents are the most cost-effective therapy and that in patients inadequately controlled on metformin plus a sulfonylurea, insulin NPH is the preferred option.
- It was noted that although insulin is the preferred option for patients with inadequate glycemic control on metformin and a sulfonylurea, an oral option is necessary for some patients.
- The Committee noted that there have been safety concerns with rosiglitazone and so another oral option may be of benefit for patients with inadequate glycemic control on metformin and a sulfonylurea. It was considered that while definitive conclusions cannot currently be made on the safety of sitagliptin, to date, signals of cardiovascular events have not been noted. Based on the most recent Periodic Safety Update Report, representing three million patient-years of exposure to sitagliptin and in a meta-analysis of 19 phase two and phase three double-blind RCTs evaluating sitagliptin (N = 10,246), no serious adverse event signals were detected.
- The Committee noted that the use of sitagliptin in patients with renal failure, congestive heart failure, and hepatic insufficiency is not recommended in the Health Canada-approved product monograph. There are additional warnings for its use in elderly patients who may experience age-related declines in renal function.
- The Committee was concerned that there is an absence of direct evidence on whether sitagliptin reduces microvascular or macrovascular outcomes and that the relationship between hemoglobin A1c and vascular outcomes may differ for new drug classes with novel mechanisms of action. It was noted that a large ongoing randomized, placebo controlled clinical trial to evaluate cardiovascular outcomes after treatment with sitagliptin may provide this evidence in the future.
- The Committee noted that although there are trials demonstrating that hypoglycemia is similar between sitagliptin and placebo when used in patients with inadequate glycemic control on metformin alone, in P035, conducted in patients with inadequate glycemic control on metformin and a sulfonylurea, hypoglycemia was statistically significantly greater in the sitagliptin group compared with the placebo group.

**CEDAC Members Participating:**

March 24, 2010: Dr. Robert Peterson (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Michael Allan, Dr. Ken Bassett, Dr. Bruce Carleton, Dr. Doug Coyle, Mr. John Deven, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Lindsay Nicolle, and Dr. Yvonne Shevchuk.


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June 16, 2010: Dr. Robert Peterson (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Michael Allan, Dr. Ken Bassett, Dr. Bruce Carleton, Dr. Doug Coyle, Mr. John Deven, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Lindsay Nicolle, Dr. Yvonne Shevchuk, and Dr. Kelly Zarnke.

**Regrets:**
March 24, 2010: Dr. Kelly Zarnke

June 16, 2010: None.

**Conflicts of Interest:**
One CEDAC member reported a conflict of interest and did not participate in the discussion or the vote.

One CEDAC member reported receiving institutional funding through Merck Frosst but no direct payments were received and funding was not related to sitagliptin, therefore, this did not preclude participation in the discussion and voting.

**About this Document:**
CEDAC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CEDAC made its recommendation.

The manufacturer has reviewed this document and has requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The Final CEDAC Recommendation neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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