



CEDAC FINAL RECOMMENDATION

SAXAGLIPTIN

(Onglyza – Bristol-Myers Squibb Canada)

Indication: Type 2 Diabetes Mellitus

Recommendation:

The Canadian Expert Drug Advisory Committee (CEDAC) recommends that saxagliptin not be listed.

Reasons for the Recommendation:

1. At the confidential price submitted, the daily cost of saxagliptin (\$████) is considerably more than the cost of a sulfonylurea, and there are no head-to-head trials comparing saxagliptin with agents from other antidiabetic drug classes in patients inadequately controlled on one agent alone. The confidential price was used to make the CEDAC recommendation and the manufacturer requested that this information be kept confidential pursuant to the CDR Confidentiality Guidelines.
2. There are no randomized controlled trials evaluating the efficacy of saxagliptin in patients failing both metformin and a sulfonylurea.

Background:

Saxagliptin has a Health Canada indication for use in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin or a sulfonylurea, when metformin or the sulfonylurea used alone, with diet and exercise, does not provide adequate glycemic control. Saxagliptin is a dipeptidyl peptidase-4 inhibitor.

The Health Canada recommended dose of saxagliptin is 5 mg once daily. It is available as a 5 mg tablet.

Summary of CEDAC Considerations:

The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of randomized controlled trials (RCTs) of saxagliptin and a critique of the manufacturer's pharmacoeconomic evaluation.

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Clinical Trials

The CDR systematic review included three manufacturer-sponsored double-blind RCTs.

Two trials evaluated saxagliptin as add-on therapy in patients with inadequate glycemic control on metformin:

- Study 014 is a published 24-week superiority trial that compared saxagliptin 5 mg daily with placebo when added to metformin. It included 745 patients with inadequate glycemic control despite stable doses of metformin (mean dose of approximately 1,800 mg daily).
- Study 056 is an unpublished 18-week non-inferiority trial that compared saxagliptin 5 mg daily with sitagliptin 100 mg daily when added to metformin. It included 801 patients with inadequate glycemic control despite stable doses of metformin (mean dose of approximately 1,800 mg daily).

One trial evaluated saxagliptin as add-on therapy in patients with inadequate glycemic control on submaximal doses of a sulfonylurea:

- Study 040 is a published 24-week superiority trial that compared saxagliptin 5 mg daily with uptitrated glyburide (mean daily dose = 14.6 mg). It included 768 patients with inadequate glucose control on submaximal doses of a sulfonylurea.

All three studies had run-in phases that differed in duration (two to four weeks). The mean baseline hemoglobin A1c ranged from 7.7% to 8.5%.

Study 014 and Study 040 were limited by high withdrawal rates (up to 37.4% in the placebo group and up to 25.1% in the saxagliptin group of Study 014) and use of last observation carried forward methodology for imputing missing data. The trials were also of short duration and intention-to-treat analyses were not conducted.

Outcomes

The primary efficacy end point in all of the included trials was the change from baseline in hemoglobin A1c. It is unclear what constitutes a minimum clinically important reduction in hemoglobin A1c.

The Committee discussed other outcomes that were defined a priori in the CDR systematic review protocol including weight change and hypoglycemia. Quality of life was not measured as an outcome in any of the included trials and none of the trials were designed to measure diabetes-related morbidity and mortality.

Results

Efficacy or Effectiveness

- In Study 014, at week 24, the change from baseline in hemoglobin A1c was –0.69% for saxagliptin plus metformin compared with 0.13% for placebo plus metformin; the adjusted mean difference in hemoglobin A1c was statistically significant (mean difference: –0.83; $P < 0.0001$).

- In Study 056, at week 18, the change from baseline in hemoglobin A1c was -0.52% for saxagliptin plus metformin compared with -0.62% for sitagliptin plus metformin in the per protocol analysis; the adjusted mean difference was 0.09% (95% CI: -0.01 to 0.20). The full analysis set found an adjusted mean difference of 0.17% (95% CI: 0.06 to 0.28); an intention-to-treat analysis was not conducted. The non-inferiority margin of $< 0.3\%$ was not exceeded at 18 weeks.
- In Study 040, at week 24, the change from baseline in hemoglobin A1c was -0.64% for saxagliptin plus glyburide compared with 0.08% for placebo plus glyburide; the adjusted mean difference in hemoglobin A1c was statistically significant (mean difference: -0.72% ; $P < 0.0001$).

Harms (Safety and Tolerability)

- Across all studies, serious adverse events were low and similar between treatment groups.
- Across the three trials there was one cardiovascular event (myocardial ischemia) in patients receiving saxagliptin and seven cardiovascular events in patients receiving placebo.
- There were no cases of pancreatitis in any of the three studies.
- One patient in the saxagliptin plus glyburide group of Study 040 reported severe hypoglycemia. There were two hypoglycemic episodes classified as serious adverse events, both of which occurred in the sitagliptin plus metformin group of Study 056; one resulted in unconsciousness. In the three studies, overall hypoglycemic events were similar between treatment groups, but definitions of hypoglycemia varied.
- In Study 014, weight change was similar between saxagliptin plus metformin and placebo plus metformin. In Study 040, over 24 weeks, the saxagliptin plus glyburide group experienced a statistically significant increase in weight of 0.5 kg compared with placebo plus glyburide, but this was not considered clinically relevant as the patients weighed approximately 75 kg at baseline.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing saxagliptin plus metformin with rosiglitazone plus metformin and pioglitazone plus metformin in patients who have failed metformin and who have failed or who have a contraindication to a sulfonylurea. The Cardiff Diabetes Model was used to estimate long-term, diabetes-related complications and associated costs. There are no head-to-head RCTs comparing saxagliptin with a thiazolidinedione in patients who have failed metformin and who have failed or who have a contraindication to a sulfonylurea; therefore, treatment effects were based on the manufacturer's mixed treatment comparison meta-analysis of RCTs in patients requiring combination therapy. The cumulative incidence of diabetes-related complications was estimated over a 40-year time horizon using equations from the United Kingdom Prospective Diabetes Study (UKPDS) 68. Decreases in patients' utilities were applied based on the diabetes-related complications and adverse events incurred (e.g., hypoglycemia, weight gain). The manufacturer reported that saxagliptin plus metformin costs less and is more effective than rosiglitazone plus metformin and is associated with an incremental cost per quality-adjusted life-year of $\$2,893$ versus pioglitazone plus metformin. When excluding the disutility associated with increases in body mass index in their sensitivity analysis, the manufacturer reported an incremental cost per quality-adjusted life-year of $\$35,349$ for saxagliptin plus metformin versus pioglitazone plus metformin.

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Based on the confidential price submitted, the daily cost of saxagliptin (5 mg; \$■■■■) 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 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:

- A therapeutic review by CADTH suggests that sulfonylurea agents are the most cost-effective therapy in patients inadequately controlled on metformin.
- The manufacturer requested listing saxagliptin in the treatment of patients with type 2 diabetes mellitus who have failed metformin and have failed or have a contraindication to a sulfonylurea. However, the trials included in the CDR systematic review were exclusively conducted in patients failing only metformin or failing only a sulfonylurea. An RCT evaluating saxagliptin compared with placebo in patients receiving both metformin and a sulfonylurea is currently ongoing.
- The relationship between hemoglobin A1c and vascular outcomes may differ for new drug classes with novel mechanisms of action. Evidence suggests that hemoglobin A1c has greater validity as an outcome for interventions when a relationship between hemoglobin A1c and patient-important outcomes, such as macrovascular outcomes, has been previously established.
- The Committee noted that the use of saxagliptin in patients with renal failure, congestive heart failure, and hepatic insufficiency is not recommended in the Health Canada product monograph. There are additional warnings for its use in elderly patients who may experience age-related decline in renal function.

CEDAC Members Participating:

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.

Regrets:

Dr. Kelly Zarnke

Conflicts of Interest:

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

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.

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

The 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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