Canadian Agency for Drugs and Technologies in Health

COMMON DRUG REVIEW

CDEC FINAL RECOMMENDATION

SAXAGLIPTIN
(Onglyza — Bristol-Myers Squibb Canada and AstraZeneca Canada)
Indication: Type 2 Diabetes Mellitus

Recommendation: The Canadian Drug Expert Committee (CDEC) recommends that saxagliptin be listed if the following clinical criterion and condition are met:

Clinical Criterion:
- 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.

Condition:
- Drug plan costs for saxagliptin should not exceed the cost of other dipeptidyl peptidase-4 (DPP-4) inhibitors.

Reason for the Recommendation:
1. In one double-blind randomized controlled trial (RCT) of patients with inadequate glycemic control on a combination of metformin and a sulfonylurea, the addition of saxagliptin resulted in a statistically significantly greater reduction in hemoglobin A1C compared with the addition of placebo.

2. At the submitted price, the daily cost of saxagliptin ($[redacted]; 5 mg) is less than the cost of sitagliptin ($2.95; 100 mg) and greater than or equal to the cost of linagliptin ($2.25 to $2.55; 5 mg).

Background:
Saxagliptin is an oral antihyperglycemic drug belonging to the DPP-4 inhibitor class. Saxagliptin is indicated for patients with type 2 diabetes mellitus to improve glycemic control in the following circumstances:
- in combination with metformin when metformin used alone, with diet and exercise, does not provide adequate glycemic control
- in combination with a sulfonylurea when a sulfonylurea used alone, with diet and exercise, does not provide adequate glycemic control

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- in combination with premixed, long or intermediate-acting insulin (with or without metformin) when premixed long or intermediate-acting insulin (with or without metformin) used alone, with diet and exercise, does not provide adequate glycemic control
- in combination with metformin and a sulfonylurea when dual therapy with these two agents, with diet and exercise, does not provide adequate glycemic control.

The recommended dose of saxagliptin is 5 mg once daily for most patients and 2.5 mg once daily for patients with moderate or severe renal impairment (creatinine clearance ≤ 50 mL / min).

Summary of CDEC Considerations:
CDEC considered the following information prepared by the Common Drug Review (CDR): a systematic review of RCTs of saxagliptin in combination with metformin and a sulfonylurea and a critique of the manufacturer's pharmacoeconomic evaluation. No patient groups responded to the CDR call for patient input. CDEC also considered the findings of the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus — Thrombolysis in Myocardial Infarction (SAVOR-TIMI) 53 study. SAVOR-TIMI was published after the CDR literature search had been completed; however, key safety and efficacy findings from this study were included in the final version of the CDR clinical review report and were discussed by CDEC.

Clinical Trials
The CDR systematic review included one RCT (Study 6) that investigated the use of saxagliptin in patients who were inadequately controlled with metformin and sulfonylurea combination therapy. Study 6 was a 24-week, multicentre, placebo-controlled, double-blind RCT involving 257 patients. The primary efficacy objective was to compare the difference in A1C levels from baseline to week 24 between saxagliptin 5 mg once daily and placebo, both in combination with metformin and a sulfonylurea.

Outcomes
Outcomes were defined in the CDR systematic review protocol. Of these, CDEC discussed the following:

- Macrovascular diabetes-related complications.
- Glycemic control — measured using A1C and fasting blood glucose.
- Changes in body weight.
- Hypoglycemia — defined as major events, minor events, and suggestive events.
- Hospitalizations for heart failure.
- Serious adverse events, total adverse events, and withdrawals due to adverse events.
- Health-related quality of life — assessed using the EQ-5D questionnaire and EQ-VAS.

The primary efficacy outcome in Study 6 was the difference in change in A1C levels from baseline to week 24 between saxagliptin 5 mg and placebo.

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Results

Efficacy

- There was a statistically significant difference favouring saxagliptin compared with placebo for change from baseline in A1C levels (adjusted mean difference [95% confidence interval (CI)] = –0.66% [–0.86% to –0.47%]; *P* < 0.0001). Subgroup analyses for age, race, and gender demonstrated findings that were similar to the overall assessment.
- The proportion of patients achieving A1C less than 7% was greater in the saxagliptin group than in the placebo group (30.7% versus 9.4%; adjusted odds ratio 9.01 [95% CI, 3.85 to 21.05]).
- Changes from baseline in EQ-5D results were similar in the saxagliptin and placebo groups.
- Mean changes from baseline in body weight at 24 weeks were 0.2 kg and –0.6 kg in the saxagliptin and placebo groups respectively (CDR calculated mean difference [95% CI] = 0.8 kg [0.3 kg to 1.3 kg]).

Harms (Safety and Tolerability)

- The proportion of patients who experienced at least one adverse event during the treatment period was lower in the saxagliptin group compared with the placebo group (63% versus 72%).
- Serious adverse events were reported for three patients (2.3%) in the saxagliptin group and seven patients (5.5%) in the placebo group.
- One patient (0.8%) in the saxagliptin group and three patients (2.3%) in the placebo group discontinued treatment due to adverse events.
- Thirteen patients (10.1%) in the saxagliptin group experienced a total of 19 hypoglycemic events and eight patients (6.3%) in the placebo group experienced a total 16 hypoglycemic events. No patients experienced a major hypoglycemic event.

Additional Studies

SAVOR-TIMI 53 was a large phase 4, placebo-controlled RCT involving 16,492 patients with type 2 diabetes and existing cardiovascular disease or multiple risk factors for cardiovascular disease. Patients were randomized to receive saxagliptin or placebo (1:1); however, investigators were permitted to adjust the participants' other medications, including antihyperglycemic drugs, at their discretion. At baseline, patients enrolled in the trial were using the following antihyperglycemic treatments: no medication (5.4%), one oral antihyperglycemic drug (25.0%), two or more oral antihyperglycemic drugs (27.7%) and/or insulin (40.9%). Patients were followed-up for a median of 2.1 years. Key safety and efficacy data were reported as follows:

- Saxagliptin was non-inferior (*P* < 0.001) but not superior (*P* = 0.99) to placebo for the primary composite outcome of cardiovascular death, non-fatal myocardial infarction, or non-fatal ischemic stroke (hazard ratio [HR], 1.00; 95% CI, 0.89 to 1.12).
- Hospitalization for heart failure was more commonly reported for patients in the saxagliptin group than in the placebo group (3.5% versus 2.8%; HR 1.27; 95% CI, 1.07 to 1.51; *P* = 0.007).
- A1C was statistically significantly lower in the saxagliptin group than the placebo group at one year (7.6% versus 7.9%), two years (7.5% versus 7.8%), and at the end of the treatment (7.7% versus 7.9%) (*P* < 0.001 for all).

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- Acute pancreatitis was reported for 0.3% of patients in the saxagliptin group and 0.2% in the placebo group (*P* = 0.77). Chronic pancreatitis was reported for 0.02% in the saxagliptin group and 0.07% in the placebo group (*P* = 0.18).

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis comparing saxagliptin with sitagliptin and linagliptin for patients with type 2 diabetes requiring third-line antidiabetic therapy. Efficacy data to support the use of a cost-minimization analysis were obtained from an indirect comparison of saxagliptin, sitagliptin, and linagliptin in terms of A1C control. Because saxagliptin, sitagliptin, and linagliptin are from the same drug class, the manufacturer assumed that other aspects of patient management were equivalent (i.e., compliance, adverse events, and discontinuation) between the three drugs and considered only drug treatment costs. The manufacturer's cost-minimization analysis was limited by the lack of head to-head RCT evidence versus the comparators. The daily drug cost of saxagliptin ($[redacted]; 5 mg) is less than that of sitagliptin ($2.95; 100 mg), but greater than or equal to the cost of linagliptin ($2.25 to $2.55; 5 mg).

Other Discussion Points:

CDEC noted the following:

- With respect to the pre-specified safety end points of SAVOR-TIMI, CDEC noted that the primary objective was achieved as saxagliptin was non-inferior to placebo for the composite end point of cardiovascular death, non-fatal myocardial infarction, or non-fatal ischemic stroke. However, CDEC noted that hospitalization for heart failure occurred more frequently in the saxagliptin group compared with the placebo group (3.5% versus 2.8%; HR: 1.27; 95% CI, 1.07 to 1.51; *P* = 0.007). It was noted that the current product monograph for saxagliptin (April 30, 2013) includes a warning that the use of saxagliptin in patients with congestive heart failure is not recommended, due to limited data for this population.
- With respect to the pre-specified efficacy end points of SAVOR-TIMI, CDEC noted that saxagliptin failed to demonstrate superiority compared with placebo for the composite end point of cardiovascular death, non-fatal myocardial infarction, or non-fatal ischemic stroke. The clinical significance of this finding was considered to be uncertain as investigators were able to adjust study participants' therapy for diabetes and cardiovascular disease during the study.
- The manufacturer requested saxagliptin be reimbursed in a manner similar to sitagliptin and linagliptin.
- Recommendations issued by CDEC in 2013 indicate that neutral protamine Hagedorn (NPH) insulin is the preferred option for patients inadequately controlled on metformin plus a sulfonylurea. In circumstances where patients are unable to use insulin as a third-line option, CDEC recommended that a DPP-4 inhibitor may be added to metformin and sulfonylurea therapy.
- Study 6 was not designed to examine the effects of saxagliptin on microvascular or macrovascular outcomes, and the relationship between A1C and vascular outcomes is uncertain.

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Research Gaps:
CDEC noted that there is insufficient evidence regarding the following:

- The observed increase in hospitalization for heart failure reported in the saxagliptin group of the SAVOR-TIMI trial. This should be further investigated to confirm the risk, estimate the magnitude of risk, and identify patient characteristics associated with the increased risk.
- Direct or indirect comparisons assessing the comparative efficacy of saxagliptin versus other antihyperglycemic drugs for the prevention of macrovascular and microvascular diabetes-related complications; such comparisons are needed.

CDEC Members:

Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

October 16, 2013 Meeting

Regrets:

None

Conflicts of Interest:

None

About This Document:
CDEC provides formulary listing recommendations or advice to CDR participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

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

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