Canadian Expert Drug Advisory Committee
Summary of Discussion

Sitagliptin (Januvia™ — Merck Frosst Canada Ltd.)
Indication — Type 2 Diabetes

Canadian Expert Drug Advisory Committee (CEDAC) Members Participating

Dr. Braden Manns (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Ken Bassett, Dr. Bruce Carleton, Dr. Malcolm Man-Son-Hing, Dr. Laurie Mallery, Ms. Nancy McColl, Mr. Brad Neubauer, Dr. Lindsay Nicolle, Dr. Robert Peterson, Dr. Dale Quest, and Dr. Kelly Zarnke.

Regrets

Dr. Michael Evans.

Conflicts of Interest

Two CEDAC members reported that they had been investigators for research studies funded by Merck Frosst Canada Ltd. As the research was not related to sitagliptin, this did not preclude their participation.

Description of Drug

Sitagliptin is the first in a new class of oral hypoglycemic agents that inhibits the enzyme dipeptidyl peptidase-4 (DPP-4). The inhibition of DPP-4 prevents the breakdown of the endogenous incretin hormone's glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide that are involved in glucose homeostasis. Sitagliptin is approved 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.

Discussion of Clinical and Pharmacoeconomic Reviews

CEDAC considered a systematic review of published and unpublished clinical studies prepared by CDR, and a CDR review of a pharmacoeconomic evaluation supplied by the manufacturer. An overview of these reviews and the complete CEDAC Final Recommendation and Reasons for Recommendation (technical and plain language versions) are available in the CDR Drug Database on the CADTH website (www.cadth.ca).

A presentation by CEDAC members and the discussion that ensued addressed the following points:

Therapeutic Rationale and Need

The prevalence of type 2 diabetes mellitus in Canada was reported as approximately 4.9% in 2005; however, prevalence rates are thought to be significantly higher due to a large population with undiagnosed disease. Type 2 diabetes mellitus is an important risk factor for coronary

artery disease, cerebrovascular disease, and peripheral vascular disease as well as renal failure, retinopathy, and neuropathy.

Clinical Trials

Four multinational double-blind randomized placebo-controlled trials in patients with type 2 diabetes mellitus were evaluated. Sitagliptin 100 mg daily was investigated in a total of 2,255 patients with glycosylated hemoglobin (HbA1c) ≥7 and ≤11% in trials ranging from 18 to 30 weeks. One trial also had an active controlled blinded extension up to 54 weeks. In three studies, patients were receiving metformin ≥1,500 mg daily with either sitagliptin or placebo. The fourth study evaluated fixed doses of metformin, either 500 mg twice daily or 1,000 mg twice daily, combined with sitagliptin or placebo; this study had a total of six arms, but two were not evaluated because the sitagliptin dose was higher than the approved dose.

Comparators

Placebo plus metformin was used as the comparator in all four trials. One of the placebo-controlled studies also included a rosiglitazone treatment arm, but it was not designed for comparison with the sitagliptin treatment arm.

Outcomes

Diabetes-related morbidity, mortality, quality of life, and health resource utilization were not measured as outcomes in any of the sitagliptin studies. Therefore, the effect of sitagliptin on these outcomes remains unknown. Preliminary mortality data, related to the intensity of glucose control with oral hypoglycemic agents, from the ACCORD and ADVANCE studies appear to be conflicting, and review of these data, when available, will be important.

Outcomes assessed included the proportion of patients achieving a HbA1c <7%, fasting plasma glucose, two-hour post-prandial glucose, changes in lipid profile, beta-cell function, adverse events, serious adverse events, withdrawal due to adverse events, hypoglycemia, and weight change. While HbA1c has been the accepted standard for measurement of glucose control, it is an inadequate surrogate marker for diabetes-related clinical events in type 2 diabetes [there have been United Kingdom Prospective Diabetes Studies (UKPDS) where reductions in HbA1c did not result in expected clinical benefits in all populations; as well as other data suggesting increased cardiovascular risk with thiazolidinediones despite durable reductions in HbA1c].

Efficacy or Effectiveness

All studies reported a statistically significant reduction in baseline HbA1c with sitagliptin plus metformin versus metformin alone, with differences ranging from -0.51% to -1.0% ($p<0.001$). The clinical value of the reduction in HbA1c was discussed with respect to the UKPDS data and safety and efficacy concerns that have been raised with rosiglitazone. While HbA1c was lower with sitagliptin than with placebo in these trials of short duration, it is unclear whether a reduction in HbA1c will be sustained over time and if it will be associated with improved clinical outcomes.

Harms (Safety and Tolerability)

There were no differences in adverse events (including hypoglycemia, weight change, gastrointestinal events), serious adverse events, withdrawal due to adverse events, or deaths between sitagliptin and placebo. There were some trends in the data suggesting an increase in infectious complications (upper respiratory tract infections, urinary tract infections). The potential for an increased risk of infection is important to note because the enzyme that sitagliptin inhibits

is also found in some white blood cells and because persons with diabetes are at increased risk of infection. Data from a monotherapy trial (with design limitations) that studied sitagliptin in patients with renal insufficiency were discussed because numerically higher rates of deaths, myocardial infarction, and atrial fibrillation associated with sitagliptin were reported.

Cost and Pharmacoeconomic Evaluation

The manufacturer submitted a confidential price for sitagliptin of [redacted], which is similar to that of rosiglitazone; however, the cost is higher than for other oral hypoglycemic agents. The cost-utility analysis using the UKPDS model from the manufacturer compared sitagliptin and metformin with rosiglitazone or pioglitazone and metformin. Because there are no relevant clinical trials versus comparators and there is limited clinical evidence about benefits and harms, especially given the novel mechanism of action, economic modelling results were felt to be highly speculative. As there are no clinical trials designed to evaluate this patient population, including with these comparators, the true cost-effectiveness of sitagliptin is uncertain.

Other Discussion Points

- No data were presented that evaluated sitagliptin in the population for which the manufacturer requested listing (patients with inadequate glycemic control despite maximal doses of metformin and intolerance to or with a contraindication for a sulfonylurea). It was noted that there are other treatment options available for this population — e.g., a patient could be switched to insulin if a sulfonylurea was contraindicated.
- All four trials were funded by the manufacturer.
- Longer-term safety data are needed.

CEDAC Recommendation

CEDAC recommends that sitagliptin not be listed.

CEDAC Reasons for the Recommendation

- While sitagliptin in combination with metformin reduced blood glucose and HbA1c compared with metformin alone in short-term trials, the effect of sitagliptin on any clinically important diabetes-related vascular outcomes has not been examined in randomized controlled trials.
- Sitagliptin is not recommended in patients with moderate to severe renal insufficiency. The long-term safety of sitagliptin is uncertain, and this is of critical importance given recent safety concerns with other oral hypoglycemic agents.
- The manufacturer submitted a confidential price for sitagliptin with a [redacted], which is more expensive than many alternative oral hypoglycemic agents (sulfonylurea agents, pioglitazone, acarbose, repaglinide). The manufacturer proposed that sitagliptin be listed on formularies with restriction to patients who have a contraindication to or are intolerant of a sulfonylurea agent. However, there is insufficient information on the effectiveness and cost-effectiveness of sitagliptin in these patients, and it is unclear what its place in therapy would be in comparison to less expensive alternative agents.

The Summary of CEDAC Discussion

This document contains a summary of the relevant discussion by CEDAC members in making the formulary listing recommendation for participating public drug plans regarding this drug. This summary is not a complete record of the proceedings of the CEDAC meeting at which the drug was considered.

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The statements, conclusions, and views expressed herein do not necessarily represent the view of Health Canada, the federal government, any provincial or territorial government, or any pharmaceutical manufacturer.

The manufacturer has reviewed this document and has requested the deletion of confidential information.