CEDAC FINAL RECOMMENDATION and REASONS for RECOMMENDATION

SITAGLIPTIN
(Januvia™ – Merck Frosst Canada Inc.)

Description:
Sitagliptin is an inhibitor of dipeptidyl peptidase IV, the first of a new class of oral hypoglycemic agents. It 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.

Dosage Forms:
100 mg tablets. The recommended dose is 100 mg daily.

Recommendation:
The Committee recommends that sitagliptin not be listed.

Reasons for the Recommendation:
1. While sitagliptin in combination with metformin reduced blood glucose and hemoglobin A1c (Hb A1c) compared to metformin alone in short term trials, randomized controlled trials (RCTs) have not examined the effect of sitagliptin on any clinically important diabetes-related vascular outcomes.

2. 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.

3. The manufacturer submitted a confidential price for sitagliptin [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.

Summary of Committee Considerations:
The Committee considered a systematic review of RCTs evaluating the combination of sitagliptin and metformin in adult patients with Type 2 diabetes mellitus and inadequate glycemic control. Four trials comparing the combination of sitagliptin plus metformin with placebo plus metformin and ranging in duration from 18 to 30 weeks met the inclusion criteria for the systematic review. One trial also included a treatment arm of rosiglitazone plus metformin but it was not designed to compare the effects of

sitagliptin with rosiglitazone. All trials reported that when compared with placebo, sitagliptin resulted in short-term statistically significant reductions in Hb A1c, with the mean difference between groups ranging from -0.51% to -1.0%. The proportion of patients achieving a target Hb A1c of <7% was also statistically significantly higher in patients treated with sitagliptin compared with placebo. No completed trials have examined clinically important outcomes of diabetes mellitus such as mortality, cardiovascular morbidity or microvascular outcomes.

The Committee also reviewed the results of extension trials with sitagliptin with follow-up from 54 to 104 weeks and these trials suggest that glycemic control with sitagliptin is attenuated with longer term use.

None of the trials reported statistically significant differences between sitagliptin and placebo in serious adverse events, severe hypoglycemic episodes, withdrawals due to adverse events, adverse events or weight gain or loss. Sitagliptin is not recommended for use in patients with moderate or severe renal insufficiency. A small placebo controlled trial of sitagliptin monotherapy in patients with renal insufficiency reported numerically higher rates of death, myocardial infarction and atrial fibrillation in patients treated with sitagliptin.

The manufacturer submitted a confidential price for sitagliptin [redacted], which is similar in price to for rosiglitazone ($2.02 to $2.88 for 4 mg to 8 mg daily) but more expensive than pioglitazone ($1.12 to $2.36 for 15 mg to 45 mg daily). Sitagliptin is also higher in cost compared to repaglinide ($0.32 to $0.68 for 0.5 mg to 4 mg), nateglinide ($0.56 to $0.60 for 60 mg to 180 mg), and acarbose ($0.76 to $1.05 for 150 mg to 300 mg). The manufacturer submitted a cost utility analysis in which they consider the treatment of adults with Type 2 diabetes mellitus who have inadequate glycemic control on maximal tolerated doses of metformin as monotherapy and who are intolerant of, or have a contraindication to a sulfonylurea agent. Sitagliptin plus metformin was reported to be associated with a cost per quality-adjusted life year (QALY) of $612 when compared to rosiglitazone plus metformin and $9,225 when compared to pioglitazone plus metformin. As there are no clinical trials designed to evaluate this patient population and with these comparators, the true cost-effectiveness of sitagliptin is uncertain.

Of Note:

1. Both published and unpublished data were reviewed and taken into consideration in making this recommendation.

2. This document has been edited to remove confidential information at the manufacturer's request in conformity with the CDR Confidentiality Guidelines.

Background:

CEDAC provides formulary listing recommendations to publicly funded drug plans. Recommendations are based on an evidence-based review of the medication's effectiveness and safety and an assessment of its cost-effectiveness in comparison to other available treatment options. For example, if a new medication is more expensive than other treatments, the Committee considers whether any advantages of the new medication justify the higher price. If the recommendation is not to list a drug, the Committee has concerns regarding the balance between benefit and harm for the medication, and/or concerns about whether the medication provides good value for public drug plans.

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