CEDAC FINAL RECOMMENDATION and REASONS for RECOMMENDATION

INSULIN GLULISINE
(Apidra – sanofi-aventis Canada Inc.)

Description:
Insulin glulisine is a rapid-acting insulin analogue with a shorter duration of action than regular human insulin. It is indicated for the treatment of adult patients with Type 1 or Type 2 diabetes mellitus (DM) where treatment with insulin is required.

Dosage Forms:
Supplied as 100 units/mL solution for subcutaneous injection (available as vials and prefilled disposable pens).

Recommendation:
The Canadian Drug Expert Advisory Committee (CEDAC) recommends that insulin glulisine be listed in a similar manner as drug plans list rapid-acting insulin analogues (i.e. insulin lispro, insulin aspart) if the cost of insulin glulisine is less than the cost of the other rapid-acting insulin analogues to the drug plans.

Reasons for the Recommendation:
1. At the submitted price, the cost of insulin glulisine is less than the cost of insulin lispro and insulin aspart listed by drug plans.

2. Clinical trials suggest that insulin glulisine is associated with similar efficacy and safety compared with other rapid-acting insulin analogues (insulin lispro, insulin aspart) and regular human insulin in Type 1 diabetes mellitus and similar efficacy and safety compared with regular human insulin in Type 2 diabetes mellitus.

Summary of Committee Considerations:
The Committee considered a systematic review of seven open-label, randomized controlled trials (RCTs) (n=4017). Four trials were conducted in patients with Type 1 DM and three trials were conducted in patients with Type 2 DM. The difference in the adjusted mean change from baseline in hemoglobin A1c (%) was the primary efficacy outcome in all trials, except for one Type 1 DM trial. None of the trials used the prefilled pen device that is available in Canada.

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Three of the four Type 1 DM trials compared insulin glulisine administered in multiple daily injections with insulin lispro or regular human insulin, using insulin glargine as basal insulin. These trials had a non-inferiority design and used a non-inferiority margin of 0.4% or 0.45% absolute change in A1c. The sample sizes ranged from 267 to 866 patients and the duration of the treatment phase ranged from 12 to 52 weeks. In the remaining trial (n= 59, 12 weeks), insulin glulisine was compared with insulin aspart, both given as continuous subcutaneous insulin infusions (CSII).

Two of the three Type 2 DM trials compared insulin glulisine administered in multiple daily injections with regular human insulin, using insulin NPH as basal insulin. Both trials had a non-inferiority design and were 26 to 52 weeks in duration. Sample sizes ranged from 876 to 890 patients. In the remaining trial (n=387, 16 weeks, superiority design), three interventions were compared: insulin glulisine administered in combination with oral antidiabetic drugs (OADs), insulin glulisine alone, and OADs alone.

In patients with Type 1 DM, insulin glulisine was shown to be non-inferior, but not superior to insulin lispro and regular human insulin for the primary outcome of mean change in A1c. There was no clinically important difference in the proportion of patients experiencing an episode of hypoglycemia or in the monthly rate of severe and nocturnal hypoglycemia when insulin glulisine was compared with other rapid-acting insulin analogues or regular human insulin. There was no statistically significant difference in the mean two-hour postprandial plasma glucose (PPG) between insulin glulisine and insulin lispro.

In patients with Type 2 DM, insulin glulisine was non-inferior to regular human insulin. Insulin glulisine was also statistically superior to regular human insulin in one trial in patients with Type 2 DM, although the absolute difference [mean difference of change in A1c (%): -0.16, 95% confidence interval -0.26 to -0.05] is not clinically meaningful. When used alone or in combination with OADs, insulin glulisine lowered A1c more than OAD alone, but at the expense of more overall and nocturnal hypoglycemic events. There was no clinically important difference in the proportion of patients experiencing an episode of severe and nocturnal hypoglycemia or in the monthly rate of severe and nocturnal hypoglycemia when insulin glulisine was compared with regular human insulin. In Type 2 DM trials, patients taking insulin glulisine had a statistically significantly lower two-hour PPG compared with regular human insulin, but the clinical significance of this difference has not been established in randomized trials.

The impact of insulin glulisine on important clinical outcomes of diabetes is unknown. The trials were not designed to measure macrovascular (e.g. ischemic heart disease, myocardial infarction, peripheral vascular disease) or microvascular complications (e.g. retinopathy, nephropathy, neuropathy).

At the submitted price, insulin glulisine costs $2.37/mL (vial) or $3.16/mL (pre-filled pen) which is less expensive than other rapid-acting insulin analogues: insulin aspart $2.69/mL (vial) or $3.58/mL (cartridge), and insulin lispro $2.58/mL (vial) or $3.44/mL (cartridge). Insulin glulisine is more expensive than regular human insulins: Humulin-R $1.89/mL (vial) or $2.53/mL (cartridge), and Novolin ge Toronto $1.94/mL (vial) or $2.54/mL (cartridge).

Of Note:

1. Both published and unpublished data were reviewed and taken into consideration in making this recommendation.
2. There are now three rapid-acting insulin analogues available. Drug plans should consider a drug class review for these agents to assess their relative effectiveness, harms, cost and place in therapy relative to regular human insulin.

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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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