CEDAC FINAL RECOMMENDATION on RECONSIDERATION and REASONS for RECOMMENDATION

INSULIN GLARGINE RESUBMISSION
(Lantus® – Sanofi-Aventis Canada Inc.)

Description:
Insulin glargine is an insulin analog indicated for once-daily subcutaneous administration for patients over 17 years of age with Type 1 or Type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) had previously recommended that insulin glargine not be listed (see notice of CEDAC Final Recommendation on insulin glargine issued on September 28, 2005). A new economic model submitted by the manufacturer was the basis for the insulin glargine resubmission. The Committee maintains its recommendation that insulin glargine not be listed.

Dosage Forms:
100 IU/mL, 10 mL vial for subcutaneous injection

Reasons for the Recommendation:
1. No new clinical trial results were considered by the Committee for this resubmission. As previously reported, 20 open-label randomized controlled trials (RCTs) lasting from 4 to 52 weeks have compared insulin glargine with NPH insulin, of which 11 were conducted in Type 1 diabetes and 9 in Type 2 diabetes. The studies did not find statistically or clinically significant differences between insulin glargine and NPH on Hemoglobin A1c (Hb A1c) in patients with either Type 1 or Type 2 diabetes.

2. Nine RCTs in Type 1 diabetes and eight RCTs in Type 2 diabetes reported on the incidence of severe symptomatic hypoglycemia. No significant differences between insulin glargine and NPH insulin were observed for this outcome in any of these RCTs.

3. Variable results were found for the incidence of overall and nocturnal hypoglycemia for both Type 1 and Type 2 diabetes. For symptomatic nocturnal hypoglycemia (confirmed and unconfirmed), 4 of 6 trials in Type 1 diabetes showed a significantly reduced number of events in the insulin glargine arm compared with NPH, yet two large trials failed to observe this difference after 1 to 7 months of follow-up. Eight of 9 studies reported the incidence of nocturnal hypoglycemia in Type 2 diabetes. Two trials did not detect a statistically significant difference between insulin glargine and NPH at 4 weeks. Six studies (from 4 to 52 weeks) found that significantly fewer patients in the insulin glargine group had nocturnal hypoglycemic events.

4. Quality of life was measured with validated instruments such as the Treatment Satisfaction and the General Well-being scales. Results were inconsistent for the Type 1 diabetes trials. There was no significant difference between groups in the Type 2 diabetes trials.

5. Hb A1c and hypoglycemic episodes need to be considered together when evaluating insulin therapy. In considering the results of all RCTs, the Committee found no convincing evidence that insulin glargine consistently led to a reduced Hb A1c with an accompanying equal or lower incidence of major hypoglycemia than other comparator insulins.

6. The pharmacoeconomic model submitted by the manufacturer was based on the assumptions that patients treated with insulin glargine experienced fewer episodes of severe and nocturnal hypoglycemia, and that the reduced fear of hypoglycemia with insulin glargine resulted in improved quality of life. This model reported that the cost per quality-adjusted life year (QALY) associated with use of insulin glargine compared with NPH insulin was $32,200 and $37,700 in Type 1 and Type 2 diabetes, respectively. The Committee felt that the model overestimated the benefits of insulin glargine in reducing hypoglycemic episodes. Moreover, the model assumed very large increments in quality of life due to the avoidance of hypoglycemia. This was based on one unpublished observational study which showed that patients who had severe hypoglycemia had lower overall quality of life. It is uncertain whether their lower quality of life was due to the hypoglycemic episodes or the fear of those episodes or because patients with severe diabetes, who are more likely to experience episodes of severe hypoglycemia, have a reduced quality of life due to the severity of their disease. Moreover, as noted, this impact on quality of life was not consistently demonstrated in the RCTs. Overall, the cost per QALY is likely to be much higher than reported by this model.

7. Insulin glargine costs $5.50 per 100 units, while NPH insulin costs $1.67 per 100 units (the dose equivalency ratio of insulin glargine to NPH insulin is approximately 1:1).

8. In summary, while the Committee acknowledged that some RCTs have reported that insulin glargine may be superior to NPH insulin in reduction of hypoglycemic episodes, it did not feel that this justified the three-fold difference in cost. In order to justify reimbursement, the Committee feels that there must be a significant reduction in the price of insulin glargine.

Of Note:

1. The Committee noted that all RCTs with insulin glargine were of open-label design. This makes the outcomes of hypoglycemic episodes, especially those unconfirmed, subject to potential reporting bias. In addition, the confounding effect of the concomitant use of bolus short-acting insulin was not clarified in these trials.

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