CEDAC FINAL RECOMMENDATION on RECONSIDERATION and REASONS for RECOMMENDATION

30% INSULIN ASPART, 70% INSULIN ASPART PROTAMINE (NovoMix™ 30 - Novo Nordisk , Canada Inc.)

Description:
NovoMix™ 30, which consists of a mixture of 30% soluble insulin aspart and 70% insulin aspart protamine crystals, is approved for the treatment of adult patients with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis.

Dosage Forms:
100 U/mL for subcutaneous injection

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that NovoMix™ 30 not be listed.

Reasons for the Recommendation:

1. The Committee considered 12 randomized controlled trials (RCTs) comparing insulin aspart 30%/insulin aspart protamine 70% (biphasic insulin aspart) with biphasic human insulin 30/70 (10 trials), biphasic insulin lispro (one trial) and insulin glargine (one trial). Eight of these trials were in patients with adult onset or type 2 diabetes and four were in mixed populations with type 1 (juvenile or insulin dependent diabetes) and type 2 diabetes. The mixed trials did not report on patients with type 1 diabetes independently; therefore the Committee could not draw any conclusions in this population.

2. In the seven RCTs in type 2 diabetes comparing biphasic insulin aspart with biphasic insulin lispro or biphasic human insulin, there were no statistically significant differences in control of Hemoglobin A1c (Hb A1c) and only one of these RCTs reported an improvement in the incidence of nocturnal hypoglycaemia with biphasic insulin aspart. None of these RCTs reported an improvement in severe hypoglycemia. In the RCT with insulin glargine, Hb A1c was reduced to a statistically significant degree in the biphasic insulin aspart group, but this was achieved with 50% higher dose of insulin at the end of the study in the biphasic insulin aspart group compared to the insulin glargine group.

3. In 3 of the 5 RCTs in type 2 diabetes that included postprandial glucose as an outcome, there were statistically significant improvements reported in measures of postprandial glucose control with biphasic insulin aspart. However, there is insufficient evidence to determine the clinical

significance of these postprandial glucose changes once the effect on Hb A1c and fasting blood glucose are accounted for.

4. The cost of biphasic insulin aspart is approximately 40% higher than that of biphasic human insulin 30/70 (~$3.25 vs $2.31 per 100 Units). In the absence of a demonstrated clinical advantage in favour of biphasic insulin aspart, the Committee concluded that this cost differential was not justified.

Of Note:

1. Insulin aspart protamine, which constitutes 70% of this fixed combination product, is not licensed in Canada as a separate drug entity and therefore has not been evaluated in comparison with established long acting insulin products such as NPH insulin.

2. The cost of biphasic insulin aspart is similar to that of biphasic insulin lispro. Public drug plans have made widely different listing decisions for biphasic insulin lispro, ranging from general benefit listing to restricted listing to no listing. The Committee recommends that the listing decisions for biphasic insulin lispro be reviewed by the drug plans.

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