Insulin lispro / insulin lispro protamine

Product:
Insulin lispro / insulin lispro protamine (Humalog® Mix 50) 50% / 50% suspension for injection

Class of drugs: Insulin

Indication:
Treatment of diabetes mellitus

Manufacturer: Eli Lilly Canada Inc.

CED Recommendation-

The CED recommended that insulin lispro / insulin lispro protamine (Humalog® Mix 50) not be listed on the ODB Formulary nor be reimbursed via the Exceptional Access Program, on the basis that there is a lack of evidence demonstrating superiority over other insulin products already listed.

Executive Officer Decision

Taking the CED's recommendation into consideration and based on a subsequent listing agreement that addresses cost and utilization, the Executive Officer decided to list insulin lispro / insulin lispro protamine (Humalog® Mix 50) on the ODB Formulary.

Status

Funding through the Ontario Public Drug Programs as a General Benefit on the ODB Formulary.

Highlights of Recommendation:

- Humalog® Mix50™ is an insulin analogue combination containing 50% insulin lispro and 50% insulin lispro protamine for diabetic patients who are mixing insulin lispro (Humalog®) and NPH insulin in a 1:1 ratio for their insulin requirements.
- Patients who were on the insulin lispro mixtures had improved blood glucose control after meals and less nocturnal hypoglycemia, with the same overall blood glucose control, compared to patients who were on human insulin mixtures.
- Although insulin analogues and their mixtures are effective in controlling blood glucose levels after meals with less nocturnal hypoglycemia, the CED noted that there is no evidence this decreases long-term complications associated with diabetes (such as high blood pressure).
- **Overall, the CED noted the lack of good quality evidence to demonstrate that insulin lispro / insulin lispro protamine mixture provides any meaningful advantages over less expensive versions of insulin and insulin mixtures already listed on the Formulary.**

Background:

Diabetes mellitus is a disease that occurs because the pancreas does not produce enough insulin (a hormone) and/or the cells in the body do not respond to insulin properly to help control the level of glucose (sugar) in the blood. With Type 1 diabetes, the body does not make insulin at all. With Type 2 diabetes, the body does not make or use insulin well.

Normally, when the body digests food, glucose enters the bloodstream as a fuel source, and insulin moves glucose from the bloodstream into cells. In diabetes, high levels of glucose remain in the bloodstream resulting in long-term health complications if left untreated. The long-term outcomes of poorly treated diabetes include heart attacks, strokes, blood vessel disease, nerve damage (neuropathy), kidney disease, blindness and foot infections/limb loss.

Patients with Type 1 diabetes are managed with insulin. Patients with Type 2 diabetes often require oral medications and/or insulin if weight loss and dietary changes on their own do not lead to improved blood glucose control.

Humalog® Mix 50™ is a combination product containing insulin lispro and insulin lispro protamine in a 1:1 ratio. Insulin lispro is the rapid-acting part to meet the requirements for blood glucose control immediately after meals and the insulin lispro protamine is the intermediate-acting part to provide late blood glucose control. Insulin lispro protamine is similar to NPH insulin.

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Detailed Discussion:

- Humalog® Mix50™ is an insulin analogue combination containing 50% insulin lispro and 50% insulin lispro protamine formulated for patients who are mixing insulin lispro and NPH insulin in a 1:1 ratio to meet their insulin requirements.
- Insulin lispro (Humalog®) and insulin lispro/insulin lispro protamine 25%/75% (Humalog® Mix25™) are listed on the ODB Formulary.
- Another insulin analogue combination product, insulin aspart/insulin aspart protamine 30%/70% is listed on the ODB Formulary.
- The manufacturer proposed that insulin lispro mixtures improve after meal blood glucose control and resulted in fewer episodes of nocturnal hypoglycemia (excessively low blood sugar over night). This claim is based on data from one randomized trial (Roach et al. *Diab Obes Metab*, 2003) which compared blood glucose control between insulin lispro mixtures to human insulin mixtures in Type 1 or 2 diabetic patients. In this trial, despite improved blood glucose control after meals and less nocturnal hypoglycemia with insulin lispro mixtures compared to human insulin mixtures, both treatment groups had the same overall blood glucose control.
- Although after meal glucose control is an important component of overall HbA1c control and prevention of vascular complications, the CED noted the lack of evidence to demonstrate that improving after meal glucose control also reduces vascular complications or other clinically relevant outcomes.
- Two meta-analyses failed to show insulin analogues improve health outcomes beyond regular human insulins:
    - Siebenhofer A et al. *Cochrane Database Syst Rev*. 2004; (4):CD003287; PMID: 15495047]
    - Banerjee S et al. *Technology Overview*. Canadian Agency for Drugs and Technologies in Health, 2007.
- The CED noted that the insulin analogues and their combinations are not necessarily appropriate for all patients with diabetes, such as patients with delayed gastric emptying.
- The cost of Humalog® Mix50™ is the same as Humalog® Mix25™ and Humalog® but is more than other insulin analogue combination products already listed on the ODB Formulary.
- **Overall, the CED noted that there is a lack of compelling evidence to demonstrate a therapeutic or safety advantage to justify the price premium for the insulin lispro/ insulin lispro protamine mixture**.

CEDAC Recommendation:

(http://www.cadth.ca/index.php/en/cdr/recommendations)

The Canadian Expert Drug Advisory Committee (CEDAC) did not review this product.

Ontario

Ministry of
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