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CADTH Reimbursement Recommendation

Human Insulin (Entuzity KwikPen)

Indication: To improve glycemic control in adults and children with diabetes mellitus requiring more than 200 units of insulin per day

Sponsor: Eli Lilly

Final recommendation: Reimburse with conditions

CADTH

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Redactions: Confidential information in this document has been redacted at the request of the sponsor in accordance with the *CADTH Drug Reimbursement Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Entuzity KwikPen?

CADTH recommends that Entuzity KwikPen should be reimbursed by public drug plans to improve glycemic control in adults and children with diabetes mellitus, if certain conditions are met.

What Are the Conditions for Reimbursement?

Entuzity KwikPen should only be reimbursed if it is initiated by a specialist with experience in treating severe insulin resistance and if the cost of Entuzity KwikPen does not exceed the least expensive basal or bolus combination insulin pens or cartridges.

Which Patients Are Eligible for Coverage?

Entuzity KwikPen should only be covered to treat patients with diabetes mellitus with unacceptable glycemic control who require more than 200 units of insulin per day, with or without other therapies.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that Entuzity KwikPen was associated with decreased hemoglobin A1C levels when administered either 2 or 3 times a day and that the overall number of injections was lower when patients used Entuzity KwikPen than when they used standard insulin treatment.
- There is no evidence to suggest Entuzity KwikPen is more effective than other basal or bolus insulins used to treat diabetes mellitus. Therefore, Entuzity KwikPen should be priced no more than the lowest cost combination of basal or bolus insulin pens or cartridges to ensure cost-effectiveness.
- The injection burden in patients with diabetes mellitus who need more 200 units of insulin per day is high. There is a potential for Entuzity KwikPen to reduce the injection burden in this patient population.
- Based on public list prices, reimbursing Entuzity KwikPen may save the public drug plans approximately $7.1 million over 3 years.

Additional Information

What Is Diabetes?

Diabetes mellitus occurs when the body does not properly use or make enough insulin, which leads to high blood glucose levels. Common symptoms include extreme fatigue, unusual thirst, frequent urination, and weight change. Approximately 3.8 million people in Canada were living with diabetes in 2020, and approximately 90% of patients have type 2 diabetes.

Unmet Needs in Diabetes

Patients who need high daily insulin doses will also need to take a lot of injections, which could be accompanied by discomfort. Although there are several treatments for diabetes mellitus, some patients still have uncontrolled disease and need other treatment options.

How Much Does Entuzity KwikPen Cost?

Treatment with Entuzity KwikPen is expected to cost approximately $3.16 per 100 IU of insulin. Assuming an average dose of 339.1 units per patient per day, the cost of U-500R insulin Entuzity KwikPen is $3,911 per patient annually.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that human insulin R 500 units/mL (hereafter referred to as U-500R) should be reimbursed to improve glycemic control in adults and children with diabetes mellitus requiring more than 200 units of insulin per day, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

The IBHC study (N = 325) was a 24-week, randomized, open-label, parallel-arm, noninferiority study in which patients with type 2 diabetes mellitus (T2DM) who required high-dose insulin therapy (201 to 600 units per day) were randomized to U-500R dosage intensification regimens of either thrice daily (n = 162) or twice daily (n = 163). Results showed no difference in the least squares (LS) mean for hemoglobin A1C at the end of 24 weeks of treatment between the groups (3 times daily: mean = 7.53%; SD = 1.1%; 2 times daily: mean = 7.41%; SD = 1.0%). There was a reduction of the LS mean for hemoglobin A1C from baseline to 24 weeks of treatment with both the 3 times daily (1.12%) and 2 times daily (1.22%) regimens. The difference between the 2 treatment groups in change from baseline to the end of 24 weeks treatment was −0.10 (95% confidence interval [CI], −0.33% to 0.12%). The 95% CI for the difference between the 2 treatment groups was within the predefined noninferiority margin of 0.4%. There was also a reduction in the number of injections per day by 2 for thrice daily and 3 for twice daily from baseline values with standard U 100 insulin treatment. The study demonstrates that U-500R may be used as part of treatment protocols to intensify insulin use in diabetes management.

Based on input from 1 patient group, the CADTH clinical expert, and 1 external clinician group, it was noted that patients with diabetes mellitus (DM) who require a total daily dose (TDD) of insulin greater than 200 units could face injection burden associated with the number and volume of injections. There is a potential for U-500R to reduce the injection burden in this patient population.

U-500R ($3,911 per patient annually, sponsor-submitted price) was less costly compared with most combinations of basal or bolus insulins ($2,577 to $6,026 per patient annually based on publicly available prices). A cost comparison was submitted based on the assumption of similar effectiveness among insulins. As such, U-500R should be no more costly than the least costly combination of basal or bolus insulin pens or cartridges currently reimbursed for patients with DM who require more than 200 units of insulin per day.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason
Initiation	
1. Patients with diabetes mellitus with unacceptable glycemic control who require more than 200 units of insulin per day, with or without other therapies.	• In the IBHC study, for patients with T2DM who required more than 200 units of insulin per day, U-500R reduced hemoglobin A1C within a 24-week period in a similar magnitude using a b.i.d. or t.i.d. regimen. There was a reduction in hemoglobin A1C from baseline to the end of treatment (P < 0.001) in both t.i.d. (1.12%) and b.i.d. (1.22%) regimens but there was no between treatment difference (t.i.d. minus b.i.d.) in change from baseline to the end of 24 weeks (−0.10%; 95% CI, −0.33% to 0.12%). • There is no biologic reason that U-500R would be less effective than U 100 in patients with other types of diabetes mellitus. • Input from the clinical expert consulted by CADTH, patient group, and external clinician group suggested that U-500R addresses an unmet need in patients with high TDD insulin requirements, in which these patients may face a burden associated with the number of injections and discomfort associated with the volume of injections.
Prescribing	
2. Treatment should be initiated by a specialist with experience in treating severe insulin resistance.	• Diabetes Canada's expert panel and CADTH's clinical expert recommend the involvement of specialist prescribers in patients with high TDD insulin requirements.
Pricing	
3. The cost of U-500R should not exceed the cost of the least expensive basal or bolus combination of insulin pens or cartridges.	• There were no trials identified that compared U-500R to a basal or bolus insulin regimen in people with diabetes requiring > U 200 insulin per day, hence the cost-effectiveness is unknown. • There is insufficient evidence to justify a cost premium for U-500R over the least expensive combination of basal or bolus insulins in pens or cartridges.

b.i.d. = twice a day; T2DM = type 2 diabetes mellitus; TDD = total daily dose; t.i.d. = 3 times a day.

Discussion Points

- CDEC noted that the primary benefit of U-500R would be to address the unmet needs of patients who are on high daily doses of insulin to have a smaller, more comfortable volume of injections and a reduced number of injections per day. This might also permit more aggressive intensification of insulin therapy to achieve better diabetes control (hemoglobin A1c levels). However, the sponsor-submitted summary of evidence contained little evidence to support meaningful improvement in patient satisfaction or health-related quality of life.
- CDEC noted that the submitted clinical trial was designed to compare twice daily with thrice daily administration of U-500R but does not inform its place in practice or compare it to other insulin regimens, including those with U 200 or U 300 insulin that might also reduce the volume of some insulin injections.

- CDEC noted the clinical expert opinion that many patients who require 200 units per day will not require U-500R. Single injections with insulin pens can deliver 60 to 80 units of U 100 insulin, 120 to 140 units of U 200 insulin, or 160 units of U 200 or U 300 insulin. U-500R has a pharmacokinetic profile that makes it more difficult to adjust and fine-tune the dosage compared with more commonly used insulins.
- CDEC discussed patient input that highlighted the difficulties associated with multiple, potentially high-volume injections associated with glycemic management in patients with a TDD greater than 200 units. Moreover, CDEC noted that the unmet need becomes more pronounced as patients require a greater TDD for glycemic control.
- CDEC discussed that the available evidence does not include patients with T1DM or children (younger than age 18). As such, direct efficacy and safety of U-500R in patients with T1DM who require a TDD of more than 200 units is not established. However, there is no biologic rationale that human insulin would not work for patients with T1DM or other types of DM.
- CDEC noted that the submitted unit price of U-500R is lower than the publicly available list prices of U-200 and U-300 formulations of brand-name insulin analogues.

Background

U-500R (Entuzity) is a biosynthetic human regular insulin at a concentration of 500 units/mL that has been investigated for the treatment of insulin-resistant patients with diabetes who require high-dose insulin (daily doses > 200 units). U-500R has a Health Canada indication to improve glycemic control in adults and children with DM who require more than 200 units of insulin per day. U-500R is reserved for the treatment of patients with diabetes who require a TDD of more than 200 units of insulin (basal and/or bolus). Each KwikPen contains 1,500 units of insulin and can deliver from 5 to 300 units per injection.

Sources of Information Used by the Committee

To make their recommendation, the Committee considered the following information:

- a review of the summary of pivotal trials submitted by the sponsor, which included 1 randomized, open-label, parallel-arm, noninferiority study of patients with T2DM who required a TDD of insulin of more than 200 units
- patient perspectives gathered by 1 patient group: Diabetes Canada
- input from public drug plans and cancer agencies that participate in the CADTH review process
- one clinical specialist with expertise diagnosing and treating patients with diabetes
- input from 1 clinician group: Diabetes Canada Professional Section
- a review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

The information in this section is a summary of input from the patient groups who responded the call for patient input, a clinical expert consulted by CADTH for the purpose of this review, the clinician group who responded to a call for clinician group input, and the public drug plans participating in CADTH drug reimbursement reviews.

Patient Input

Patient input was provided by Diabetes Canada, a national health charity representing Canadians living with diabetes or prediabetes (www.diabetes.ca). Diabetes Canada used an online survey, conducted between January 29 and February 12, 2021, of people from across Canada of all ages with T1DM or T2DM and their caregivers, to gather patient perspectives on the disease, the drug under review (U-500R), and expectations for new drug therapies in this country. A total of 48 people completed the survey: 26 T1DM, 19 T2DM, and 3 caregivers (1 for T1DM and 2 for T2DM).

The majority of patients expressed how challenging, preoccupying, time-consuming, and worrisome it is to live with diabetes. Patients characterized diabetes as a burden, a condition that must be dealt with 24/7 and 365 days a year with no breaks and no holidays or time off. Patients requiring a high daily dosage of insulin expressed concerns about the frequency of injections and the discomfort associated with large-volume injections.

Keeping blood glucose at satisfactory level while avoiding low blood glucose are the most important outcomes for patients surveyed by Diabetes Canada. Another important outcome for these patients was reducing complications. Ten patients (21%) reported having experience with the drug under review. In general, patients had good experiences with U-500R because it is easier to use, there is no need to measure blood glucose levels as frequently, and it has a quicker and longer blood glucose controlling effect compared with regular U-100 insulin.

Clinician Input

According to the clinical expert consulted by CADTH, insulin-resistant patients who need large insulin doses require large volumes to be injected to achieve these doses, and 2 or more injections at a time may be needed to reach the required dose if standard U-100 is used. Thus, patients who require large doses of insulin 4 times per day may require 8 or more injections per day. For these patients, U-500R could be used as a monotherapy or in combination with other non-insulin treatments such as oral medications. U-500R is used to improve glycemic control for diabetes patients with high insulin resistance. By the time a patient with T2DM requires insulin, other treatments, such as lifestyle changes and medications, have usually been tried. U-500R would be used as an alternative insulin and insulin regimen for patients requiring more than 200 units of insulin per day in either basal or basal-bolus regimens.

Clinician Group Input

Clinician group input was received on behalf of clinician members from the Diabetes Canada Professional Section regarding the reimbursement review of U-500R. Views expressed by the clinician group were in agreement with the input of the clinical expert consulted by CADTH and will be discussed in more details later in this document.

Drug Program Input

Input from drug programs explored the questions of generalizability to patients with T1DM and the lack of comparators in the clinical studies.

Clinical Evidence

Description of the Study

The CADTH clinical review was based on a summary of clinical evidence provided by the sponsor with the CADTH tailored review process, focused on the pivotal B5K-US-IBHC (IBHC) study. IBHC was a 24-week, randomized, open-label, parallel-arm, noninferiority study in which participants with T2DM requiring high-dose insulin therapy (201 to 600 units per day) were assigned to either thrice daily or twice daily U-500R dosing regimens. Participant randomization was stratified by site, baseline hemoglobin A1C, TDD, and pioglitazone use. The primary objective of this study was to compare the change in hemoglobin A1C from baseline after 24 weeks of treatment in 2 treat-to-target algorithms of U-500R (3 times a day versus 2 times a day) in adult subjects with T2DM who did not achieve adequate glycemic control on high-dose U-100 insulins and/or analogues with or without oral antidiabetic agents.

A total of 325 adult patients with T2DM (162 in the thrice daily arm and 163 in the twice daily arm) were randomized in the IBHC study. The mean age of study participants was 55.4 (SD = 9.8) years, and more than half (n = 172; 52.9%) were male. The main race groups were White (n = 266; 81.8%) and Black (n = 40; 12.3%); Hispanics were listed as the main ethnic group (n = 62; 19.1%). Overall, 260 participants (80.0%) completed the study; 132 of 162 (81.5%) completed the thrice daily treatment and 128 of 163 (78.5%) completed the twice daily treatment. The most frequent reasons for discontinuation included protocol violations (n = 27; 8.3%) and participant decision (n = 17; 5.2%). A total of 8 participants (2.5%) discontinued because of an adverse event (AE) and 1 (0.3%) because of death. There was no significant difference between the percentage of participants who discontinued from the thrice daily or twice daily groups for any reason. At baseline, patients were already on a mean of 287 units of insulin for a median of 5 injections per day (range = 2 to 10), with a mean hemoglobin A1C of 8.7% (SD = 1.0%). Patients were able to increase their insulin dose (51 to 55 units/day) with fewer injections to achieve significantly improved glycemic control using treat-to-target algorithms.

Efficacy Results

No difference in LS mean for hemoglobin A1C at the end of 24 weeks of treatment was found between the groups (3 times daily: mean = 7.53%; SD = 1.1; 2 times daily: mean = 7.41%; SD = 1.0). There was a reduction of LS mean for hemoglobin A1C from baseline to 24 weeks of treatment for both the thrice daily (1.12%, SD = 0.08) and twice daily (1.22%, SD = 0.08) regimens. The difference between the 2 treatment groups in change from baseline to the end of 24 weeks of treatment was −0.10, (95% CI, −0.33% to 0.12%). This 95% CI for the difference between the 2 treatment groups was within the predefined noninferiority margin of 0.4%. There was also a reduction in the number of injections per day by 2 for the 3 times per day group and 3 for the 2 times per day group from baseline values with standard U-100 insulin treatment.

Harms Results

Serious adverse events (SAEs) during this trial were related to patients' advanced diabetes disease state, as indicated by long diabetes duration and high pre-existing comorbidities at baseline. Incidence of SAEs and treatment-emergent AEs (TEAEs) were comparable between the thrice daily and twice daily groups. The only TEAEs that differed significantly between treatment groups were pain in extremity (3 times daily: n = 3; 1.9%; 2 times daily: n = 10; 6.1%) and arthralgia (3 times daily: n = 7; 4.3%; 2 times daily: n = 1; 0.6%). AEs requiring U-500R discontinuation (n = 4; 2.5% in each group) were also balanced. No AEs were recorded for dosing errors related to administration of U-500R via U-100 insulin syringes. Both treatment with U-500 and titration algorithms were safe alternatives for patients who had failed glycemic control on high-dose and/or high-volume U-100 insulin therapy. There were no significant differences in severe hypoglycemia between the thrice daily and twice daily regimens, although higher non-severe hypoglycemia and weight gain was observed in the twice daily group than in the thrice daily group. An increase in insulin dose (TDD increase of 41.4% for the thrice daily group and 34.5% for the twice daily group) from baseline to 24 weeks of treatment and weight gain accompanying reduction in hemoglobin A1C (0.47 kg per 1% reduction in hemoglobin A1C for the thrice daily group and 1.31 kg per 1 reduction in hemoglobin A1C for the twice daily group) were observed. One death was reported in the twice daily arm of the trial; the patient suffered a presumed prolonged severe hypoglycemia that led to coma and death.

Economic Evidence

Cost and Cost-Effectiveness

At a submitted price of $94.79 per package of two 3-mL pre-filled pens, the cost per 100 units of U-500R insulin is $3.16. Assuming an average dose of 339.1 units per patient per day, the cost of U-500R insulin is $3,911 per patient annually. The sponsor submitted a cost comparison assessing U-500R insulin compared on a 1-to-1 basis with combinations of 50% of each basal insulin analogue and 50% of a weighted average cost of bolus insulin analogues, with and without considering the cost of insulin needles. U-500R insulin was also compared with combinations of 50% of bolus and 50% basal human insulins.

CADTH identified the following limitations with the sponsor's submitted cost comparison:

- the assumption of clinical similarity to other available insulins was uncertain
- the total daily use of insulin increased during the U-500R insulin clinical trial, but the sponsor assumed 1:1 unit replacement between U-100 and U-500R insulin for their cost calculations
- a newly reimbursed insulin comparator was missing (Admelog-brand insulin lispro)
- the price of insulin needles was overestimated and not always applicable.

CADTH reanalyses included considering the daily dose of insulin units used in the IBHC trial at baseline of U-100 insulin comparators and at week 24 for U-500R insulin, comparing each combination of a basal and bolus insulin rather than an overall weighted average of bolus insulin analogues, and the inclusion of Admelog-brand insulin lispro. U-500R insulin was less expensive than most combinations of U-100 bolus and basal insulin analogue

products (annual cost range: $4,277 to $6,026 per patient) but was more expensive than the combination of subsequent entry products Admelog-brand insulin lispro and Basaglar-brand insulin glargine (annual cost: $3,771 per patient) as well as combinations of human insulin (annual cost range: $2,577 to $3,415 per patient). For public plans that reimburse insulin needles, a small additional savings may be realized due to the decreased number of injections required per day with the use of U-500R insulin.

At the submitted price and based on the mean dose at week 24 in the pivotal IBHC trial, the annual cost of U-500R insulin is $3,911 per patient annually. When comparators are assumed to be dosed as at baseline in the pivotal IBHC trial, U-500R insulin is less expensive than combinations of originator brands of basal and bolus insulin analogues, but more expensive than combinations of human insulin or the 2 available subsequent entry insulin analogues. The submitted price of U-500R insulin would need to be reduced by 3.6% for its annual cost to be equivalent to that of the least expensive combination of insulin analogues, and 14% or 34% to be equivalent to the least expensive combination of human insulins in cartridges or vials, respectively. The costs and savings associated with the use of U-500R insulin are uncertain due to a lack of comparative clinical evidence to basal or bolus insulin regimens. Additionally, these incremental costs or savings are based on publicly available list prices and may not reflect actual prices paid by Canadian public drug plans

Budget Impact

The sponsor estimated the incremental budget savings of reimbursing U-500R insulin to be $6,900,122 over 3 years. CADTH identified limitations with the submitted budget impact analysis and undertook reanalyses which estimated the incremental budget savings of reimbursing U-500R insulin were $7,155,636 over 3 years. CADTH noted the budget impact is sensitive to the number of eligible patients, with more patients increasing the estimated savings, whereas savings are reduced when higher daily doses of U-500R insulin are required relative to the lower concentration insulins being replaced.

Members of the Canadian Drug Expert Committee

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Sally Bean, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Dr. Kerry Mansell, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Meeting date: June 16, 2021

Regrets: 3 expert committee members did not attend.

Conflicts of interest: None