CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

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.

Recommendation: Reimburse with Conditions

Version: 1.0
Publication Date: July 2021
Report Length: 8 Pages

Single Technology

CADTH

Human Insulin (Entuzity KwikPen — Eli Lilly)

Therapeutic Area: Diabetes mellitus

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that Human Insulin R 500 units/mL (hereafter referred to as U500-R) 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 where patients with T2DM who required high dose insulin therapy (201 to 600 units per day) were randomized to either thrice daily (TID, n = 162) or twice daily (BID, n = 163) U500-R dosage intensification regimens. Results showed no difference in least squares (LS) mean (SD) of HbA1c at the end of 24 weeks treatment between groups: TID=7.53% (1.1) and BID=7.41% (1.0). There was a reduction of LS mean in HbA1c from baseline to 24 weeks of treatment with both TID (1.12%) and BID (1.22%) regimens. The difference between the two treatment groups in change from baseline to the end of 24 weeks treatment was -0.10, with 95% confidence interval (CI) of -0.33% to 0.12%. This 95% CI for the difference between the two treatment groups was within the pre-defined noninferiority margin of 0.4%. There was also a reduction in the number of injections/day by 2 and 3 for TID and BID, respectively, from baseline values with standard U100 insulin treatment. The study demonstrates that U500-R may be used as part of treatment protocols to intensify insulin use in diabetes management.

Based on input from one patient group, the CADTH clinical expert, and one external clinician group, it was noted that patients with DM who require a total daily dose (TDD) greater than 200 units could be facing injection burden associated with the number and volume of injections. There is a potential for U500-R to reduce the injection burden in this patient population.

U500-R ($3,911 per patient annually, sponsor submitted price) was less costly compared with most combinations of basal/bolus insulins ($2,577–$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, U500-R should be no more costly than the least costly combination of basal/bolus insulin in pens or cartridges currently being reimbursed for patients with diabetes mellitus requiring 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,patients with T2DM who require more than 200 units of insulin per day, U500-R reduced HbA1c within a 24 week period in a similar magnitude using a BID or TID regimen. There was a reduction in HbA1c from baseline to the end of treatment (p<0.001) in both TID (1.12%) and BID (1.22%) regimens but there was no between treatment (TID minus BID) difference in change from baseline to the end of 24 weeks (-0.10%; 95% CI: -0.33%, 0.12%). • There is no biologic reason that U500-R would be less effective than U100 in patients with other types of diabetes mellitus. • Input from the clinical expert consulted by CADTH, patient group, and external clinician group suggested that U500-R addresses an unmet need in patients with high total daily dose (TDD) insulin requirements, where these patients may face a burden associated with the number of injections, and discomfort associated with the volume of injections.
Prescribing	
1. 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	
1. The cost of U500-R should not exceed the cost of the least expensive basal/bolus combination of insulin pens/cartridges.	• There were no trials identified that compared U500-R to a basal/bolus insulin regimen in people with diabetes requiring >U200 insulin per day, hence the cost effectiveness is unknown. • There is insufficient evidence to justify a cost premium for U500-R over the least expensive combination of basal/bolus insulins in pens or cartridges.

Discussion Points

- CDEC noted that the primary benefit of U500-R might be to address the unmet needs of patients on high daily doses insulin to have smaller, more comfortable volume of injections and reduced number of injections per day. This might also permit more aggressive intensification of insulin therapy to achieve better diabetes control (A1c). 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 BID with TID administration of U500-R but does not inform its place in practice or compare it to other insulin regimens, including those with U200 or U300 insulin that might also reduce the volume of some insulin injections.
- CDEC noted the clinical expert opinion that many patients requiring 200 units per day will not require U500-R. Single injections with insulin pens can deliver 60-80units of U100 insulin, 120-140 units of U200 insulin or 160 units of U200 or U300 insulin. U500-R has a pharmacokinetic profile that makes it more difficult to adjust and fine tune dosage compared to 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 TDD greater than 200. Moreover, CDEC noted that the unmet need becomes more pronounced as patients require greater TDD t for glycemic control.
- CDEC discussed that the available evidence does not include patients with T1DM or in children (under age 18). As such, direct efficacy and safety of U-500R in patients with T1DM who require more than 200 TDD is not established. However, there is no biological rationale that human insulin would not work for patients with T1DM or other types of diabetes mellitus.
- CDEC noted that the submitted price of U500-R is lower than the publicly available list prices of brand-name insulin analogues, including those of U200 and U300 formulations.

Background

U-500R (Entuzity) is a biosynthetic human regular insulin at a concentration of 500 units per mL that has been investigated for the treatment of insulin resistant patients with diabetes requiring high-dose insulin (daily doses >200 units). U-500R has a Health Canada indication to improve glycemic control in adults and children with diabetes mellitus requiring more than 200 units of insulin per day. U-500R is reserved for the treatment of patients with diabetes requiring total daily doses 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. This included one randomized, open-label, parallel-arm, noninferiority study of patients with T2DM requiring and insulin TDD over 200 units.
- Patient perspectives gathered by one 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 one 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 provided by the patient groups who responded to CADTH's call for patient input, from a clinical expert consulted by CADTH for the purpose of this review, from clinician group who responded to CADTH call for clinician groups input, and from the public drug plans participating in CADTH drug reimbursement review.

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 from people 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 vast majority of patients expressed how challenging, preoccupying, time-consuming, and worrisome it is to live with diabetes. Patients characterize 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 sugar is the most important outcomes for patients surveyed by Diabetes Canada. Other important outcomes for these patients are reducing complications. Ten patients (21%) reported having experience with the drug under review. In general, patients had good experience with U-500R because it is easier to be used, no need to measure blood sugar levels as frequently, and has quicker and longer blood sugar controlling effect, as compared with regular U-100 insulin.

Clinician input

The clinical expert consulted by CADTH suggested for insulin resistant patients who need large insulin doses, large volumes need 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 requiring 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 >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 is a 24-week, randomized, open-label, parallel-arm, noninferiority study where participants were assigned to either thrice daily (TID) or twice daily (BID) U-500R dosing regimens in patients with T2DM requiring high dose insulin therapy (201 to 600 units per day). Participant randomization was stratified by site, baseline HbA1c, total daily dose (TDD), and pioglitazone use. The primary objective of this study was to compare the change in HbA1c from baseline after 24 weeks of treatment in 2 treat-to-target algorithms of U-500R (TID vs. BID) in adult subjects with T2DM who did not achieve adequate glycemic control on high-dose U-100 insulins/analogs with or without OADs.

A total of 325 adult patients with T2DM (162 in TID arm and 163 in BID arm) were randomized in the IBHC study. Mean and standard deviation (SD) of age of study participants were 55.4 (9.8) years and more than half (172, 52.9%) were male. Main race groups were white (266, 81.8%) and black (40, 12.3%), with Hispanics listed as a main ethnic group (62, 19.1%). Overall, 260 subjects (80.0%) completed the study, with 132 of the 162 subjects (81.5%) completed the TID treatment, and 128 of the 163 subjects (78.5%) completed the BID treatment. The most frequent reasons for discontinuation included protocol violations (27, 8.3%) and subject decision (17, 5.2%). A total of 8 subjects (2.5%) discontinued because of an adverse event (AE) and 1 (0.3%) because of death. There was no significant difference between the percentages of subjects who discontinued from TID and BID for any reason. At baseline, patients were already on a mean of 287 units of insulin, a median of 5 injections per day (range, 2 to 10), and mean (SD) HbA1c 8.7% (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 least squares (LS) mean (SD) of HbA1c at the end of 24 weeks treatment was found between groups: TID=7.53% (1.1) and BID=7.41% (1.0). There was a reduction of LS mean in HbA1c from baseline to 24 weeks of treatment with both TID (1.12%) and BID (1.22%) regimens. The difference between the two treatment groups in change from baseline to the end of 24 weeks treatment was -0.10, with 95% confidence interval (CI) of -0.33% to 0.12%. This 95% CI for the difference between the two treatment groups was within the pre-defined noninferiority margin of 0.4%. There was also a reduction in the number of injections/day by 2 and 3 for TID and BID, respectively, 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 as well as treatment-emergent AEs (TEAEs) were comparable between TID and BID. The only individual TEAEs differing significantly between treatment groups were pain in extremity (1.9% [n = 3], TID; 6.1% [n = 10], BID; P = 0.049) and arthralgia (4.3% [n = 7], TID; 0.6% [n = 1], BID; P = 0.04). AEs requiring U-500R discontinuation (2.5% of patients [n = 4] for 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/high-volume U-100 insulin therapy. The regimens showed no significant differences in severe hypoglycemia between TID and BID, although a higher non-severe hypoglycemia and weight gain in BID than in TID was observed. An increase in insulin dose (TDD increase of 41.4% for TID and 34.5% for BID) from baseline to 24 weeks of treatment and weight gain accompanying reduction in HbA1c (0.47 kg per 1% reduction in HbA1c for TID and 1.31 kg per 1 reduction in HbA1c for BID) were observed. One death was reported in the BID 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 to combinations of 50% of each basal insulin analog and 50% of a weighted average cost of bolus insulin analogs, with and without considering the cost of insulin needles. U-500R insulin was also compared to 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 IHBC 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 analogs; and, the inclusion of Admelog-brand insulin lispro. U-500R insulin was less expensive than most combinations of U-100 bolus and basal insulin analog 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 which reimburse insulin needles, a small amount of 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 analogs, but more expensive than combinations of human insulin or the two available subsequent entry insulin analogs. 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 analogs, 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/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 saving of reimbursing U-500R insulin to be $6,900,122 over three-years. CADTH identified limitations with the submitted budget impact analysis and undertook reanalyses which estimated the incremental budget saving of reimbursing U-500R insulin were $7,155,636 over three-years. CADTH noted the budget impact is sensitive to the number of eligible patients, with more patients increasing the estimated savings, while savings are reduced when higher daily doses of U-500R insulin are required relative to the lower concentration insulins being replaced.

CDEC Members

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.

June 16, 2021 Meeting

Regrets

3 expert committee members did not attend.

Conflicts of Interest

None

CADTH

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