CADTH

CADTH REIMBURSEMENT REVIEW

Clinician Input

HUMAN INSULIN (Entuzity KwikPen)

(Eli Lilly Canada Inc.)

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

February 22, 2021

CADTH Reimbursement Review
Clinician Group Input Template

CADTH Project Number	SR0672-000
Generic Drug Name (Brand Name)	Entuzity KwikPen
Indication	To improve glycemic control in adults and children with diabetes mellitus requiring more than 200 units of insulin per day
Name of the Clinician Group	Diabetes Canada Professional Section
Author of the Submission	[redacted]
Contact information	Name: [redacted] Title: [redacted] Email: [redacted] Phone: [redacted]

1. About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

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Diabetes Canada is a national health charity representing over 11 million Canadians living with diabetes or prediabetes. The priorities of our mission are diabetes prevention, care and cure. Our focus on research and policy initiatives helps us to deliver impact at a population level, and our partnerships broaden our reach in communities across the country. We drive excellence in disease management by putting practical, evidence-based tools into the hands of health-care providers. We advocate for environments that make the healthy choice the easy choice. We continue our search for a cure, as well as for better prevention and treatment strategies, by funding the work of innovative scientists. In 1921, Canada changed diabetes for the world with the discovery of insulin. In 2021, we will change the world for those affected by diabetes through healthier communities, exceptional care and high-impact research. For more information, please visit: www.diabetes.ca.

Professional members are an important part of the diabetes community. The Diabetes Canada Professional Section is comprised of clinicians and health-care professionals, researchers, academics and students working or studying in the field of diabetes. The Professional Section offers the opportunity for members to connect and collaborate with one another, provides the newest information on the prevention and management of diabetes in Canada, and gives access to resources and tools that help support practice.

2. Information Gathering

Please describe how you gathered the information included in the submission.

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Feedback was solicited from clinician members of Diabetes Canada's Professional Section. Interested parties provided responses to the questions in the clinician group input template by e-mail. These responses were collated to form the content for the submission.

3. Current treatments

3.1. Describe the current treatment paradigm for the disease

Focus on the Canadian context.

Please include drug and non-drug treatments.

Drugs without Health Canada approval for use in the management of the indication of interest may be relevant if they are routinely used in Canadian clinical practice. Are such treatments supported by clinical practice guidelines?

Treatments available through special access programs are relevant.

Do current treatments modify the underlying disease mechanism? Target symptoms?

Response:

Type 2 diabetes is a disorder of insulin resistance and relative insulin deficiency. To minimize the development of diabetes-related complications, achieving and maintaining near-normal blood glucose levels is an important goal in the vast majority of patients, but at the same time, so too is minimizing hypoglycemia and the burden of the disease treatment. Non-pharmacologic treatments include behaviour interventions such as good nutrition, regular physical activity and healthy body weight. There are a number of pharmacologic options as well that address both insulin resistance and the relative insulin deficiency. The current treatment paradigm requires both non-pharmacologic and pharmacologic treatments to achieve glycemic and other targets. Insulin is one of the available pharmacologic options and can be used in patients throughout their diabetes journey. However, some patients, despite the use of multiple therapies, require very high doses of insulin per day because of their insulin resistance and glycemic control can be suboptimal as a result.

4. Treatment goals

4.1. What are the most important goals that an ideal treatment would address?

Examples: Prolong life, delay disease progression, improve lung function, prevent the need for organ transplant, prevent infection or transmission of disease, reduce loss of cognition, reduce the severity of symptoms, minimize adverse effects, improve health-related quality of life, increase the ability to maintain employment, maintain independence, reduce burden on caregivers.

Response:

An ideal treatment would lessen diabetes complications, independent of its glucose-lowering properties. If that is not possible, then an ideal treatment would lower glucose levels with minimal hypoglycemia and

decreased patient burden (e.g., fewer injections, greater comfort).

5. Treatment gaps (unmet needs)

5.1. Considering the treatment goals in Section 4, please describe goals (needs) that are not being met by currently available treatments.

Examples:

- *Not all patients respond to available treatments*
- *Patients become refractory to current treatment options*
- *No treatments are available to reverse the course of disease*
- *No treatments are available to address key outcomes*
- *Treatments are needed that are better tolerated*
- *Treatment are needed to improve compliance*
- *Formulations are needed to improve convenience*

Response:

Some people living with type 2 diabetes have marked insulin resistance, either due to an underlying syndrome (e.g., certain lipodystrophies) or due to obesity. Those individuals require high doses of insulin to overcome that resistance and bring down their blood glucose levels. Those doses often exceed 200 units per day. When using the usual concentration of insulin (100 units/mL), that is equivalent to injecting more than 2 mL of liquid under the skin, which is problematic. Multiple injections at the same time are needed to administer the dose, the amount of liquid under the skin is uncomfortable and, most concerning, the absorption of the insulin is not as predictable because of the large volume. Entuzity, which provides insulin in a 500 unit/mL concentration, allows people to self-administer much larger doses of insulin in a smaller volume, which is more comfortable and more effective.

5.2. Which patients have the greatest unmet need for an intervention such as the drug under review?

Would these patients be considered a subpopulation or niche population?

Describe characteristics of this patient population.

Would the drug under review address the unmet need in this patient population?

Response:

Those people living with type 2 diabetes who are currently requiring more than 200 units per day to achieve glycemic targets represent the population with the greatest unmet need.

6. Place in therapy

6.1. How would the drug under review fit into the current treatment paradigm?

Is there a mechanism of action that would complement other available treatments, and would it be added to other treatments?

Is the drug under review the first treatment approved that will address the underlying disease process rather than being a symptomatic management therapy?

Would the drug under review be used as a first-line treatment, in combination with other treatments, or as

a later (or last) line of treatment?

Is the drug under review expected to cause a shift in the current treatment paradigm?

Response:

Entuzity would replace the existing insulin therapies for appropriate patients since it possesses both basal and bolus properties. It would allow patients to use fewer injections of insulin and simplify the regimen to replace two different kinds of insulin (basal and bolus) with a single type. It can be used in combination with other antihyperglycemic therapies, as is currently occurring with other insulins.

The following testimonial demonstrates Entuzity's role in the current treatment paradigm:

"I am a clinical endocrinologist…I started using Humalog U-500 when it was still special order through [the] Health Canada Special Access Program and only available in vials and administered with syringes. My first patient had type B severe insulin resistance syndrome and…maxed out on 1,800 units of insulin per day. That patient has been off of insulin for eight years now after receiving his treatment. With the 1,800 units/day and the vial and syringe method, the patient was still only taking four injections per day. Subsequently…I started using U-500 on significantly insulin resistant patients (none with type B), first through the Health Canada Special Access Program and subsequently in the form of Entuzity when it became commercially available".

6.2. Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with the drug under review. Please provide a rationale from your perspective.

If so, please describe which treatments should be tried, in what order, and include a brief rationale.

Response:

It would be appropriate for patients to be placed on the usual insulin therapies (100 u/mL, 200 u/mL or 300 u/mL concentrations) first and be found to have insulin requirements greater than 200 units per day. In the case of type 2 diabetes, these patients should also be placed on metformin, a GLP-1 receptor agonist and an SGLT2 inhibitor and maintained on these medications, if tolerated, to improve their insulin sensitivity and/or lower insulin requirements. However, access to all of these medications may not be possible depending on provincial formularies. After being placed on the usual insulin therapies and accompanying therapies, if glycemic control remains inadequate or the number of injections/volume intolerable, then Entuzity would be appropriate.

6.3. How would this drug affect the sequencing of therapies for the target condition?

If appropriate for this condition, please indicate which treatments would be given after the therapy has failed and specify whether this is a significant departure from the sequence employed in current practice.

Would there be opportunity to treat patients with this same drug in a subsequent line of therapy? If so, according to what parameters?

Response:

This would not affect the sequencing of other therapies, as it would be a substitute for existing insulin therapy in a patient requiring more than 200 units per day who is not achieving glycemic targets.

6.4. Which patients would be best suited for treatment with the drug under review?

Which patients are most likely to respond to treatment with the drug under review?

Which patients are most in need of an intervention?

Would this differ based on any disease characteristics (e.g., presence or absence of certain symptoms, stage of disease)?

Response:

Patients requiring more than 200 units per day of insulin who are continuing to struggle to achieve glycemic targets or find the volume of insulin/number of injections required intolerable would be best suited for treatment with Entuzity. If access is available and there are no contraindications, patients should be placed on metformin, a GLP-1 receptor agonist and an SGLT2 inhibitor, then Entuzity added, if they still require more than 200 units per day of insulin. Additionally, patients who are living with obesity or weighing over 100 kg and requiring more than 2 units/kg/day of insulin could also benefit from Entuzity.

6.5. How would patients best suited for treatment with the drug under review be identified?

Examples: *Clinician examination or judgement, laboratory tests (specify), diagnostic tools (specify)*

Is the condition challenging to diagnose in routine clinical practice?

Are there any issues related to diagnosis? (e.g., tests may not be widely available, tests may be available at a cost, uncertainty in testing, unclear whether a scale is accurate or the scale may be subjective, variability in expert opinion.)

Is it likely that misdiagnosis occurs in clinical practice (e.g., underdiagnosis)?

Should patients who are pre-symptomatic be treated considering the mechanism of action of the drug under review?

Response:

Patients best suited for this treatment are those requiring more than 200 units of insulin per day despite the concomitant use of metformin, a GLP-1 receptor agonist and an SGLT2 inhibitor (assuming there is access and no contraindication).

6.6. Which patients would be least suitable for treatment with the drug under review?

Response:

The least suitable patients would be those requiring less than 200 units per day of insulin.

6.7. Is it possible to identify those patients who are most likely to exhibit a response to treatment with the drug under review?

If so, how would these patients be identified?

Response:

There is no way to identify those who are most likely to respond.

6.8. What outcomes are used to determine whether a patient is responding to treatment in clinical practice?

Are the outcomes used in clinical practice aligned with the outcomes typically used in clinical trials?

Response:

Those who are responding to therapy will require fewer insulin injections, have greater injection site comfort and improved hemoglobin A1c.

6.9. What would be considered a clinically meaningful response to treatment?

Examples:

- *Reduction in the frequency or severity of symptoms (provide specifics regarding changes in frequency, severity, and so forth)*
- *Attainment of major motor milestones*
- *Ability to perform activities of daily living*
- *Improvement in symptoms*
- *Stabilization (no deterioration) of symptoms*

Consider the magnitude of the response to treatment. Is this likely to vary across physicians?

Response:

Those who are responding to therapy will require fewer insulin injections, have greater injection site comfort and improved hemoglobin A1c.

6.10. How often should treatment response be assessed?

Response:

Hemoglobin A1c can be assessed every 3 months and, when stable, at 6 month intervals.

6.11. What factors should be considered when deciding to discontinue treatment?

Examples:

- *Disease progression (specify; e.g., loss of lower limb mobility)*
- *Certain adverse events occur (specify type, frequency, and severity)*
- *Additional treatment becomes necessary (specify)*

Response:

Treatment can be discontinued if the patient is experiencing increased hypoglycemia despite dose adjustments.

6.12. What settings are appropriate for treatment with the drug under review?

Examples: Community setting, hospital (outpatient clinic), specialty clinic

Response:

This is appropriate for any outpatient setting.

6.13. For non-oncology drugs, is a specialist required to diagnose, treat, and monitor patients who might receive the drug under review?

If so, which specialties would be relevant?

Response:

Entuzity should be initiated and monitored by a practitioner with expertise in diabetes management. Health-care providers who prescribe and manage patients on Entuzity comment that dosing can be "tricky" at times, given that U-500 has unique kinetics and is generally given without basal insulin. It is believed to be much safer as Entuzity than it was in the vial, but should not be encouraged for use by inexperienced clinicians. Patients taking Entuzity should be followed by a care team that includes diabetes educators, who can provide additional teaching, training and support to ensure safety and optimal outcomes on the medication.

7. Additional information

7.1. Is there any additional information you feel is pertinent to this review?

Response:

Practitioners have generally found better results in their patients on Entuzity, improved convenience with the medication and lower overall cost to the patient (compared to a program with insulin analogues).

8. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   Diabetes Canada had no outside assistance to complete this submission.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   Diabetes Canada had no outside assistance to collect or analyze any information used in this submission.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician that contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

   Diabetes Canada receives unrestricted educational grants from, among others, manufacturers/vendors of medications, supplies, and devices for diabetes and its complications. These funds help the organization support community programs and services for people living with diabetes and contribute to research and advocacy efforts across Canada. No sponsor was involved in soliciting input for or developing the content of this submission.

   Please see the attached list of Diabetes Canada's financial contributors.

Declaration for Clinician 1

Clinician Information	
Name	*Alice YY Cheng*
Position	*Endocrinologist; Chair of Professional Section of Diabetes Canada*
Date	*13-02-2021*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Eli Lilly	☐	☐	☒	☐
Sanofi	☐	☐	☐	☒
Novo Nordisk	☐	☐	☐	☒
Boehringer Ingelheim	☐	☐	☐	☒
AZ, Merck, Janssen, HLS Therapeutics	☐	☐	☒	☐
Abbott	☐	☒	☐	☐
Bayer, Dexcom, Medtronic, Novartis	☒	☐	☐	☐

Declaration for Clinician 2

Clinician Information	
Name	*David Miller*
Position	*Endocrinologist, Vancouver Island Health Authority*
Date	*16-02-2021*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Eli Lilly	☒	☐	☐	☐

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Last updated: February 2021

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