

Reimbursement Recommendation

Teplizumab (Tziel)

Indication: To delay the onset of stage 3 type 1 diabetes in adult and pediatric patients 8 years of age and older with stage 2 type 1 diabetes

Sponsor: Sanofi-aventis Canada Inc.

Final recommendation: Do not reimburse

Summary

What Is the Reimbursement Recommendation for Tzield?

Canada's Drug Agency (CDA-AMC) recommends that Tzield not be reimbursed by public drug plans to delay the onset of stage 3 type 1 diabetes (T1D) in adult and pediatric patients aged 8 years or older with stage 2 T1D.

Why Did CDA-AMC Make This Recommendation?

- Evidence from 1 clinical trial demonstrated that Tzield delayed the time of progression to stage 3 T1D by approximately 2 years, compared to placebo, in adults or children aged 8 years or older with a diagnosis of stage 2 T1D. While this delay could mean extra time without insulin and fewer lifestyle burdens, it's unclear if it leads to long-term health benefits, such as reducing risk of macrovascular and microvascular complications in stage 3 T1D. Short-term safety data show that Tzield can cause side effects, including serious ones, and there is no information on long-term safety or its impact on quality of life.
- Patient groups emphasized the potential value in delaying stage 3 T1D, and indicated that there is a need for treatments that reduce complications and improve health-related quality of life (HRQoL). The Canadian Drug Expert Committee (CDEC) acknowledged that delaying stage 3 T1D could mean extra time without insulin and with fewer lifestyle burdens. However, CDEC noted that the evidence does not show whether the delay improves outcomes like reducing insulin burden, lowering complications, or helping with education and psychological adjustment. Overall, it remains uncertain whether the potential benefits outweigh the risks and unknowns.

Additional Information

What Is T1D?

T1D occurs when the pancreas makes little or no insulin, which leads to high blood sugar levels. Patients in earlier stages (1 or 2) of T1D have no noticeable symptoms. Eventually, almost all patients in stage 2 T1D progress to stage 3 T1D. Common symptoms in this stage include unusual thirst, frequent urination, feeling very hungry, losing weight without trying, feeling tired, mood changes, and blurry vision, and patients need life-long insulin replacement therapy. People with stage 1 or stage 2 T1D often remain undiagnosed until they reach stage 3. In Canada, approximately 32 new cases of T1D per 100,000 individuals were diagnosed in 2019.

Summary

Unmet Needs in T1D

Patients with stage 2 T1D need treatments that reduce the risk of diabetic complications and improve HRQoL. Patients also need treatment that can be offered earlier when T1D develops, when currently there are no treatments approved for patients at stage 2 T1D.

How Much Does Tziel Cost?

Treatment with Tziel is expected to cost \$257,740 per patient for a single course of treatment, based on the Health Canada–recommended dosage.

Recommendation

CDEC recommends that teplizumab not be reimbursed to delay the onset of stage 3 type 1 diabetes (T1D) in adult and pediatric patients 8 years of age and older with stage 2 T1D.

Rationale for the Recommendation

Evidence from 1 phase II, randomized, placebo-controlled trial, the TN-10 trial (N = 76; 44 received teplizumab and 32 received placebo), demonstrated that after a median follow-up of 24.5 months, treatment with teplizumab likely resulted in delaying the time of progression to stage 3 T1D by approximately 2 years, compared to placebo, in adults or children aged 8 years or older with a diagnosis of stage 2 T1D. However, it remains uncertain whether this delay translates into long-term clinical benefits, such as reduced risk of macrovascular and microvascular complications in stage 3 T1D. Short-term safety data indicate that teplizumab may result in more adverse effects, including serious adverse events, and long-term safety data are lacking. Additionally, the impact of teplizumab on HRQoL — both during the delay period and after progression to stage 3 T1D — remains unknown.

Input from patient groups highlighted several unmet needs, including reducing the risk of diabetic complications, improving HRQoL, and earlier intervention in the T1D disease continuum, emphasizing the potential value of delaying progression to stage 3 and the associated need for daily insulin. CDEC acknowledges the potential for meaningful benefits based on individual psychosocial considerations, such as time free from the burdens of glucose monitoring, lifestyle changes, and insulin management. However, CDEC deemed that the submitted evidence was insufficient to support a recommendation to reimburse, given that there is no evidence on the comparative burdens of glucose monitoring, lifestyle changes, and insulin management. In addition, there is uncertainty about the evidence supporting the long-term clinical relevance of delaying progression to stage 3 T1D by 2 years. Specifically, the sponsor did not assess whether this delay affects key treatment objectives, such as reducing the burden of insulin therapy once stage 3 T1D develops, lowering the risk of complications, or providing clinically valuable time for education and psychological adjustment, particularly given that the onset of this chronic condition remains inevitable. At this time, it remains unclear whether a 2-year delay in progression to stage 3 T1D is sufficient to outweigh the unknown comparative benefits and risks of treatment with teplizumab and the potential risk of adverse events.

Discussion Points

- **Reconsideration request:** The sponsor requested a reconsideration of the initial draft recommendation not to reimburse teplizumab to delay the onset of stage 3 T1D in adult and pediatric patients aged 8 years or older with stage 2 T1D. There were 4 issues outlined by the sponsor in the request for reconsideration that were discussed by CDEC:

- The sponsor expressed concerns regarding the committee's interpretation of the findings, especially that the submitted evidence was deemed insufficient at this time to support a positive recommendation.
- According to the sponsor, patients included in the studies were representative of those seen in clinical practice in Canada, especially regarding family history and ethnicity.
- The sponsor argued that the delay in progression is suggestive of clinically meaningful effectiveness.
- Finally, the sponsor highlighted that identifying suitable candidates for teplizumab therapy could be done in the absence of a population-level screening program for stage 2 T1D.
- **Unmet need:** During the initial and reconsideration meetings, CDEC discussed patient group input that emphasized the importance of having time to prepare (physically, emotionally, and logistically) for the intensive management needs associated with stage 3 T1D. They acknowledged that, for those unaware of their asymptomatic stage 2 status, the transition to stage 3 can feel abrupt and distressing, and is often coupled with the acute trauma of life-threatening diabetic ketoacidosis (DKA). Patients also indicated that there is a need for treatments that reduce the risk of diabetic complications and improve HRQoL. Within this context, the committee reflected on the current lack of a disease-modifying treatment option for stage 2 T1D and considered how the potential for teplizumab to delay stage 3 onset may provide valuable time for patients and their caregivers to prepare for stage 3. In addition, the committee discussed the potential benefits of increased availability and access to robust screening and identification of stage 2 T1D as a means of addressing this unmet need. However, the magnitude of the unmet need remains uncertain due to the absence of systematic screening for stage 2 T1D. Furthermore, approximately 85% of individuals diagnosed with T1D do not have a family history, further complicating early identification and intervention efforts. During the reconsideration meeting, CDEC acknowledged the feedback received from the clinician and patient groups who stated that teplizumab may address an important unmet need by prolonging the time spent without stage 3 T1D. Patients indicated that the burden of T1D includes self-management by the individual and/or caregivers, mental health challenges, and out-of-pocket costs, all of which are substantial and emotionally overwhelming. Clinicians highlighted that diabetes affects the daily lives of those with T1D, physically, psychologically, and emotionally, and that its burden extends beyond the clinical outcomes of reducing long-term diabetes complications. However, CDEC noted that whether teplizumab addresses the identified unmet needs remains uncertain based on the current limitations in the evidence.
- **Patient and clinician group feedback on the draft recommendation:** During the reconsideration meeting, CDEC reviewed feedback on the draft recommendation from 2 patient groups and 4 clinician groups. This feedback emphasized the psychosocial burden of T1D and the meaningful value of delaying its onset. Patient groups expressed a desire for treatments that would alleviate this burden and increase the life-years spent without stage 3 T1D. In addition, clinicians emphasized that teplizumab may address an important unmet need, as the prevalence and severity of long-term diabetes complications increase with earlier disease onset and/or longer diabetes duration. During

the reconsideration meeting, CDEC recognized the perspectives and experiences of the clinician groups and individual clinicians who treat T1D, particularly with respect to the potential efficacy of teplizumab, as well as the limitations seen with other treatment options. Furthermore, as previously indicated, CDEC acknowledged the unmet therapeutic need in the management of T1D. However, CDEC could not establish that the available evidence adequately substantiates that teplizumab meets the identified needs, given the limitations identified.

- Limitations in generalizability and trial design of the TN-10 trial:** During the initial meeting, CDEC noted that the small sample size of the TN-10 trial (N = 76) led to imbalances in baseline characteristics between treatment groups, a limitation that increases the risk of bias and may inflate effect sizes. Additionally, the study population may not reflect real-world clinical practice in Canada. Most participants were white, limiting generalizability to racially and ethnically diverse populations. The proportion of adults was also lower than expected in clinical settings. Furthermore, the trial's restrictive exclusion criteria, such as the exclusion of individuals with abnormal blood counts or liver function, may not align with what could happen in clinical practice. In addition, only individuals with a family history of stage 3 T1D were eligible for enrolment, although the majority of people (approximately 85%) who develop T1D do not have a family history. T1D is a relatively common chronic condition; however, CDEC acknowledged the challenges of identifying patients with stage 2 T1D and that a larger, more representative study was not conducted. CDEC noted that the limitations in the TN-10 trial raise concerns about both the internal and external validity of the trial and the extent to which its findings can be applied to routine clinical care. During the reconsideration meeting, CDEC noted that while certain patient characteristics may affect generalizability, not all of them are effect modifiers that influence interpretation of the findings. The clinical experts noted to CDEC that family history is not expected to alter disease trajectory or treatment response, nor is it correlated with prognosis in stage 2 T1D or the occurrence of adverse outcomes. The experts indicated, however, that more information is needed for a better understanding of the treatment effect of teplizumab in a more diverse population. In addition, the experts noted that the presence of comorbidities is frequent and that a broad population may be eligible to receive treatment with teplizumab in clinical practice, even though patients with comorbidities were excluded from the TN-10 trial. This exclusion could affect the real-world effectiveness and safety of teplizumab.
- Clinical meaningfulness of the results:** During the initial meeting, CDEC noted that the TN-10 trial demonstrated that teplizumab delayed progression to stage 3 T1D by approximately 2 years, a benefit considered clinically meaningful by the clinical experts, particularly for pediatric patients. In children, this delay may support physical and emotional development and provide families with valuable time to prepare for the demands of stage 3 T1D. Clinical experts and patient groups emphasized that, in the absence of a cure for T1D, delaying disease progression could offer meaningful benefits for individuals with stage 2 T1D, including improved HRQoL, reduced burden of insulin therapy, lower risk of acute complications (e.g., hyperglycemia, DKA), and more time for education, monitoring, and psychological adjustment. However, there was a lack of data for the effects of teplizumab on these important goals. Current evidence does not confirm whether the delay in progression translates into long-term improvements in outcomes such as reduced risk of

microvascular or macrovascular complications. Additionally, the impact of teplizumab on HRQoL — both during the delay period and after progression — remains unknown. During the reconsideration meeting, CDEC acknowledged the patient and clinician input received by CDA-AMC, which reported that a 2-year delay represents an important, meaningful, and valued impact on patients diagnosed with stage 2 T1D and their caregivers, based on presumed individual psychosocial considerations. The current evidence on teplizumab, however, does not provide information on the impact of a 2-year delay on the overall disease trajectory or on longer-term clinical outcomes and complications. CDEC noted that there is a lack of data for the effects of teplizumab on important treatment goals (such as reduced burden of insulin therapy once patients reach stage 3 T1D and lower risk of acute complications) and for the clinical value of time for education and psychological adjustment in the context that the development of this chronic condition is inevitable.

- Long-term efficacy and safety:** During the initial meeting, CDEC discussed the results from the extended follow-up of the TN-10 trial, which indicated that at the 80.46-month follow-up time point, the proportion of patients who did not have stage 3 T1D was 36% (16 of 44 patients) in the teplizumab group and 12.5% (4 of 32 patients) in the placebo group. However, CDEC noted several limitations that affect the interpretation of these findings. Harm outcomes were not assessed in the long-term extension, and missing data handling was not reported. The open-label design introduced potential bias, as patient behaviour may have influenced outcomes. Furthermore, detailed efficacy results (such as between-group differences and confidence intervals [CIs]) were not reported, limiting the ability to fully evaluate the durability of effect. These evidence gaps, particularly the absence of long-term safety data in a larger generalizable population, constrain confidence in the long-term efficacy and safety of teplizumab. During the reconsideration meeting, CDEC noted that teplizumab is a first-in-class therapy for patients with stage 2 T1D, and noted the challenges to obtain long-term data at this stage. However, the lack of long-term effectiveness and safety data limits the comprehensive evaluation of the benefit and risk of teplizumab in the study population, especially considering that teplizumab delays but does not prevent the onset of a chronic disease with which individuals will live with over decades.
- Impact on HRQoL:** During the initial and reconsideration meetings, HRQoL was identified by both patient groups and clinicians as a clinically important outcome, particularly given the substantial psychosocial burden of stage 3 T1D (especially for young children and for families of all patients). Daily disease management requires constant attention to insulin needs, diet, and stress, significantly impacting patients' well-being. However, HRQoL was not assessed in the TN-10 trial, leaving the effect of teplizumab on patients' HRQoL — whether they progress to stage 3 T1D or not — unknown. This gap limits the ability to fully evaluate the patient-centred value of treatment.
- Ethics and equity considerations:** During the initial meeting, the committee reflected on the ethical implications of the evidentiary limitations identified, including how these gaps affect interpretation of benefit for patients and caregivers. In particular, the absence of HRQoL data and long-term outcome measures complicated assessment of whether the potential benefits of delayed progression justify the risks and burdens of treatment, especially in a pediatric population. The committee also discussed

the ethical implications of the trial's limited diversity and narrow eligibility criteria. Specifically, they noted that the underrepresentation of racialized populations in the TN-10 trial, alongside the exclusion of individuals without a family history of T1D — a group that comprises around 85% of the population with T1D — constrains both the generalizability and fairness of using this evidence base to support decisions on public funding. These limitations were seen as challenging in the context of known inequities in T1D diagnosis, care, and outcomes across racial and socioeconomic groups. During the reconsideration meeting, CDEC discussed the potential benefit of population-level screening for stage 2 (or earlier) T1D, especially for young children. In the absence of such screening, patients without a family history of T1D are unlikely to be identified before symptomatic onset of stage 3 disease. However, the absence of a population-level screening program was not used by the committee to support their rationale for recommending not to reimburse teplizumab.

Background

T1D is a chronic, progressive autoimmune condition resulting from the destruction of insulin-producing beta cells in the pancreas, culminating in chronic hyperglycemia and reliance on exogenous insulin for survival.

T1D progresses as a continuum across 3 stages. Stages 1 and 2 are asymptomatic and characterized by the presence of at least 2 diabetes-related autoantibodies, with or without development of abnormal glucose tolerance. Patients who advance to stage 2 T1D have a 100% lifetime risk of stage 3 T1D, which is characterized by overt hyperglycemia, presence of 2 or more diabetes-related autoantibodies, and the development of typical clinical symptoms and signs of diabetes requiring the use of life-long exogenous insulin replacement therapy. With stage 3 disease, hypoglycemia and hyperglycemia can escalate to serious, life-threatening complications, including altered consciousness and coma, if not immediately managed. DKA is another serious complication of diabetes that may lead to stupor, coma, and in the absence of effective treatment, death. DKA can lead to further long-term complications and is a common cause of diabetes-related mortality in T1D. Patients with T1D have compromised HRQoL compared to the general population. Caregivers of children with T1D also bear the negative impact of the disease and its management, with parents of children with diabetes reporting lower parenting satisfaction than parents of healthy children. In Canada, the incidence rate of stage 3 T1D among adolescents and young adults (aged 10 to 24 years) was 31.89 per 100,000 individuals in 2019. People with stage 1 or stage 2 T1D often remain undiagnosed until they reach stage 3, by which time there has been a substantial loss in the number of beta cells and endogenous insulin production. Currently, there is no extensive early-detection testing program for the general population available in Canada. There is uncertainty regarding the incidence and prevalence of patients with stage 2 T1D in Canada.

The current management for stage 2 T1D is education and glucose monitoring, and there are no treatments approved for patients at this stage. There is a substantial unmet need to treat patients for T1D earlier in the continuum of disease and delay the onset of stage 3 disease. Delaying the onset of stage 3 T1D for patients with stage 2 T1D would extend the period of life free from the daily burden of diabetes management. This

approach would also mitigate the complications associated with diagnosis, insulin use, and the long-term effects of stage 3 T1D, such as the risk of cardiovascular disease.

Teplizumab has been approved by Health Canada to delay the onset of stage 3 T1D in adult and pediatric patients aged 8 years and older with stage 2 T1D. It is available as a 2 mg/2 mL single-use vial, and the dosage recommended in the product monograph is through IV infusion, using body surface area-based dosing, once daily for 14 consecutive days, as follows:

- day 1: 65 mcg/m²
- day 2: 125 mcg/m²
- day 3: 250 mcg/m²
- day 4: 500 mcg/m²
- days 5 through 14: 1,030 mcg/m².

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 phase II, randomized, double-blind, placebo-controlled trial, the TN-10 trial (N = 76), in patients with stage 2 T1D, and 1 long-term extension study
- patients' perspectives gathered through a joint patient group submission by Breakthrough T1D Canada and Diabetes Canada
- input from public drug plans that participate in the reimbursement review process
- input from 3 clinical specialists with expertise diagnosing and treating patients with T1D
- input from 1 clinician group, the Canadian Society for Endocrinology and Metabolism
- a review of the pharmacoeconomic model and report submitted by the sponsor
- a review of relevant ethical issues related to teplizumab
- information submitted as part of the sponsor's request for reconsideration (described subsequently)
- feedback on the draft recommendation.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

A joint patient group submission was received from Breakthrough T1D Canada and Diabetes Canada. Breakthrough T1D Canada is a national patient advocacy and research funding organization specifically dedicated to people in Canada living with T1D. Diabetes Canada is a national health charity representing people in Canada who are affected by diabetes. Breakthrough T1D Canada and Diabetes Canada gathered

information through an online survey conducted from January 10, 2025, to February 14, 2025. The survey had 463 respondents.

The majority of respondents (n = 351; 83%) living with stage 3 T1D indicated that they were either extremely concerned or very concerned about the progression of T1D, its impact on their daily life over time, and the amount of time they needed off work to deal with diabetes. According to the patient group input, the only available treatment for patients with T1D is external insulin, which is often accompanied by medical risks, suboptimal clinical outcomes, and a heavy burden on patients.

Most of the respondents in the patient groups (n = 216; 54%) indicated that they felt there were significant gaps in the availability of immunotherapy medications for T1D, such as teplizumab. At the time patient input was collected, teplizumab was not available in Canada. Patients reported that any delay in disease progression would improve their overall well-being and decrease the risk of diabetic complications, and that for young children, a delay of 2 to 3 years in progressing to stage 3 T1D would have a significant impact. Eight survey respondents had experience with teplizumab and noted that teplizumab delayed the onset of stage 3 T1D, helped to maintain independence, and improved their physical and mental health. Despite the limited experience with teplizumab in Canada, the patient groups stated that having access to teplizumab and its potential to delay the onset of stage 3 T1D would have a significant positive impact on lives.

The patient groups clarified that the indication for teplizumab is stage 2 T1D. Autoantibody testing is performed via a blood test and associated assay; however, this is not yet a standard practice in Canada, and the cost of screening for the health care systems in Canada is unclear. The majority of respondents (n = 292; 70%) indicated that they would like to participate in screening for T1D-associated autoantibodies if medications to delay the onset of T1D were available.

Clinician Input

Input From Clinical Experts Consulted for This Review

The information in this section is based on input received from a panel of 3 clinical specialists consulted by CDA-AMC for the purpose of this review.

The clinical experts consulted for this review indicated that the most significant unmet need for patients with stage 2 T1D is that currently, there are no treatments targeting this patient population. In addition, no population-based screening program for stage 2 disease is in place in Canada; thus, the clinical experts indicated that the majority of patients are currently unaware that they have stage 2 disease. Given that almost all patients in the early stages of T1D will progress to stage 3 T1D (according to the literature, patients who advance to stage 2 T1D have a 100% lifetime risk of progressing to stage 3 T1D), the clinical experts noted that the goals of treatment for patients with stage 2 T1D would be to delay the onset of stage 3 T1D, to prevent stage 3 T1D in those identified as being at high risk, to prevent serious complications associated with the transition from stage 2 to stage 3 disease (e.g., hyperglycemia, potential DKA), and to alleviate patients' anxiety and stress.

The clinical experts indicated that teplizumab would be the first and only disease-modifying therapy to delay the onset of stage 3 T1D in this patient population. The experts also noted that teplizumab would be used as first-line treatment and would not be combined with other treatments. Given the lack of alternative therapies, the experts noted that the use of teplizumab would cause a shift in the current treatment paradigm, being a first-in-class medication for stage 2 T1D. However, structured screening programs would need to be put in place to identify the patients who could benefit from this treatment.

The clinical experts noted that patients with stage 2 T1D are best suited for treatment with teplizumab. The experts highlighted the challenges in identifying patients with stage 2 T1D in clinical practice, given that T1D at this stage is asymptomatic, and a population-based screening program for T1D has not been implemented in Canada. In current clinical practice, stage 2 T1D is usually identified in people at higher risk of developing T1D, such as those with a family member living with T1D; however, the majority of people (approximately 85%) diagnosed with T1D do not have a family history. The clinical experts also raised concerns about the challenges of such a national screening program. Diabetes-related autoantibody testing is needed to identify patients who are suitable for treatment with teplizumab. The challenge is that the current autoantibody screening tests in Canada vary in sensitivity and specificity, as well as availability and accessibility. Also, it is unknown whether this program is cost-effective, or at what age screening should be performed.

The clinical experts consulted for this review indicated that in general, outcomes used in clinical practice to determine patients' response to treatment include delay in onset of stage 3 T1D (assessed every 3 to 6 months), prevention of DKA in those who progress to stage 3 T1D, and patients' HRQoL, in particular psychosocial well-being.

The clinical experts consulted for this review noted that initial IV infusions of teplizumab may be associated with immediate adverse events (AEs) (although the therapy is generally safe without serious AEs [SAEs] occurring), and therefore may result in treatment discontinuation, while discontinuation due to long-term effects of immunosuppression therapies are less of a concern with teplizumab in clinical practice given the short course of treatment and current evidence available.

The clinical experts indicated that a specialist (typically a pediatric or adult endocrinologist, but this can also include an internist or pediatrician) would be required to diagnose, treat, and monitor patients with stage 2 T1D who may receive teplizumab. In addition, the experts emphasized the importance of appropriate infrastructure and clinical expertise to provide IV infusions in hospital settings and monitor patient safety during the 14-day infusions.

Clinician Group Input

CDA-AMC received 1 submission from the Canadian Society for Endocrinology and Metabolism (CSEM). CSEM is a professional organization of academic and community-based endocrinologists and researchers that advocates for excellence in endocrinology research, education, and patient care in Canada.

The clinician group agreed with the clinical experts consulted by CDA-AMC that there are no available therapies that modify the disease progression of T1D in Canada and that insulin therapy is required for the treatment of T1D when patients are diagnosed at stage 3. The clinician group and clinical experts consulted

by CDA-AMC agreed that a major unmet need is the lack of treatments to delay the onset of stage 3 T1D. CSEM added that ongoing demands of managing T1D and the associated emotional burden can also impair patients' quality of life.

The clinician group noted that teplizumab is the first approved disease-modifying therapy for T1D and would be used alone as the first-line treatment to delay the onset of stage 3 T1D in adults and children (aged ≥ 8 years) with stage 2 T1D, and could shift the treatment paradigm from solely managing blood glucose levels to modifying the underlying disease process.

All clinicians noted that a major challenge would be identifying individuals with stage 2 T1D because it is asymptomatic and population screening for T1D has not yet been implemented. The clinical experts consulted by CDA-AMC added that clinicians are most likely to identify stage 2 T1D in people with a family history of T1D, but most people diagnosed with T1D do not have a family history.

The clinician group and the clinical experts consulted by CDA-AMC agreed that the important outcome is a delay in progress from stage 2 to stage 3 T1D, which should be assessed by measuring fasting plasma glucose, oral glucose-tolerance test (OGTT), or hemoglobin A1C every 3 to 6 months.

CSEM explained that discontinuation of teplizumab therapy should be considered if severe or persistent AEs occur, or if disease progression occurs.

According to the CSEM, teplizumab administration requires a multidisciplinary team with expertise in the treatment and monitoring of patients with T1D. Outpatient infusion centres, hospital-based infusion clinics, or specialty pediatric endocrine or diabetes centres are preferred. These locations must have the necessary infrastructure to monitor patients for AEs.

Drug Program Input

Input was obtained from the drug programs that participate in the reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a recommendation for teplizumab:

- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- care provision issues
- system and economic issues.

The clinical experts consulted for the review provided advice on the potential implementation issues raised by the drug programs.

Clinical Evidence

Systematic Review

Description of Studies

The evidence included in this review consisted of 1 phase II, double-blind, placebo-controlled randomized controlled trial (RCT), the TN-10 trial (N = 76). The purpose of this study was to evaluate the efficacy and safety of teplizumab for delaying the onset of stage 3 T1D (also known as clinical T1D) in adults or children aged 8 years or older with a diagnosis of stage 2 disease. These patients were relatives of individuals with a confirmed diagnosis of stage 3 T1D. Eligible patients were randomly assigned to receive either teplizumab (n = 44) or placebo (n = 32) in a double-blind manner. The primary efficacy end point of this study was time from randomization to stage 3 T1D diagnosis. In addition, changes in levels of C-peptide and hemoglobin A1C, as well as harms, were evaluated. This study was projected to last between [REDACTED] and [REDACTED] years. At baseline, patient characteristics were generally comparable between the 2 treatment groups. Of the 76 patients, the median age was 14 years in the teplizumab group and 13 years in the placebo group. There were 29 patients (65.9%) who were younger than 18 years in the teplizumab group, compared to 26 patients (81.3%) in the placebo group. Before enrolment, all patients were positive for at least 2 autoantibodies, while 75% of all patients were positive for 3 or more. The teplizumab and placebo groups were similar in baseline glucose and hemoglobin A1C levels. There were some imbalances in the proportion of patients who were first-degree relatives of siblings with T1D and the presence of certain autoantibodies. In this study, patients who were not diagnosed with T1D had OGTTs at 3 months after randomization and then every 6 months thereafter until the study cut-off date or withdrawal. If the patients progressed to stage 3 T1D, they were not followed up any further.

At the end of the TN-10 study, patients who had not progressed to stage 3 T1D were continuously followed for a median of 80.46 months. Outcomes assessed during this period of time included time from randomization to stage 3 T1D, and changes in levels of C-peptide and hemoglobin A1C. Patients were unblinded to the treatment assignment during the extended follow-up.

Efficacy Results

After a median follow-up of 24.5 months, stage 3 T1D was diagnosed in 20 of 44 participants (45%) in the teplizumab group and 23 of 32 participants (72%) in the placebo group. The median time from randomization to stage 3 T1D diagnosis was 49.5 months (95% CI, 32.1 months to not estimable [NE]) in the teplizumab group and 24.9 months (95% CI, 9.5 months to 48.6 months) in the placebo group, with a between-group difference of 24.6 months (95% CI not available). Because the patients who progressed to stage 3 T1D no longer underwent further assessments, the time from randomization to stage 3 T1D was longer than the median follow-up time. The hazard ratio (HR) obtained from the Cox proportional hazards model was 0.41 (95% CI, 0.22 to 0.78; P = 0.0066). The clinical experts consulted for this review indicated that the delay of approximately 2 years in the onset of stage 3 T1D with teplizumab versus placebo is considered clinically meaningful. However, the clinical experts noted that the long-term effects of teplizumab on lowering the risks of macrovascular and microvascular events remain unclear.

Change from baseline in the level of C-peptide reflects beta cell function in patients with T1D. C-peptide levels were collected during OGTT and testing was no longer performed when patients were diagnosed with stage 3 T1D. At 2 years of treatment, results of C-peptide testing were available for approximately [REDACTED] % of the study participants (i.e., those who remained in the study because they had not been diagnosed with stage 3 T1D); the 2 hour mean of the C-peptide area under the concentration-time curve (AUC) was [REDACTED] (standard deviation [SD] = [REDACTED]) nmol/L in the teplizumab group and [REDACTED] (SD = [REDACTED]) nmol/L in the placebo group. The clinical importance of this between-group difference was unclear. In addition, analyses of C-peptide levels were exploratory in the TN-10 study; therefore, the evidence can only be considered supportive. Furthermore, in patients who progressed to stage 3, it is unknown how teplizumab would impact patients' C-peptide levels once they are diagnosed with T1D.

Change from baseline in the level of hemoglobin A1C was reported in the TN-10 study. At 2 years of treatment, the mean hemoglobin A1C was [REDACTED] % (SD = [REDACTED]) in the teplizumab group and [REDACTED] % (SD = [REDACTED]) in the placebo group, which is similar to the baseline values. In this study, hemoglobin A1C values were considered to be within the normal range; given that patients ceased to be followed after the onset of stage 3 T1D as per the protocol of the TN-10 trial, the consistent and normal hemoglobin A1C levels in both treatment groups were an expected result.

HRQoL was considered a clinically important outcome by the patient groups and clinicians. However, HRQoL was not assessed in the current submission; therefore, the effect of teplizumab on patients' HRQoL, in particular psychosocial well-being, is unknown.

Harms Results

At a median follow-up of 24.5 months, [REDACTED] % of patients in the teplizumab group and [REDACTED] % in the placebo group had experienced at least 1 AE. In the teplizumab group, the most commonly reported AEs were lymphopenia (72.7%), leukopenia ([REDACTED] %), rash pruritic ([REDACTED] %), and nasopharyngitis ([REDACTED] %). Grade 3 treatment-emergent adverse events (TEAEs) occurred in [REDACTED] patients ([REDACTED] %) in the teplizumab group and [REDACTED] patients ([REDACTED] %) in the placebo group.

Treatment-emergent SAEs occurred in [REDACTED] patients ([REDACTED] %) in the teplizumab group and [REDACTED] ([REDACTED] %) in the placebo group. The SAEs reported in the teplizumab group included [REDACTED]
[REDACTED]
[REDACTED] case of [REDACTED]
[REDACTED] was reported as an SAE in the placebo group.

[REDACTED] patients discontinued from study treatment because of TEAEs, including [REDACTED] increased ALT ([REDACTED] %) in the teplizumab group and [REDACTED] cases of hyperbilirubinemia ([REDACTED] %) in the placebo group.

No patient died during the study.

[REDACTED] patients ([REDACTED] % with grade 3 events of cellulitis, gastroenteritis, pneumonia, and wound infection) in the teplizumab group had an adverse event of special interest (AESI), while [REDACTED] from the placebo group reported AESIs. There were no grade 3 or higher liver function abnormalities, grade 3 or

higher neutropenia, grade 4 or higher cytokine-release syndrome or lymphocyte count lower than 500 mm³ for 7 days or longer reported at the data cut-off date of November 30, 2018.

The clinical experts consulted for this review noted that most AEs were manageable and that there were no unusual safety issues observed.

Critical Appraisal

In the TN-10 study, there were some imbalances between the 2 treatment groups in patients' baseline characteristics, such as the proportion of patients younger than 18 years, proportion of siblings with T1D, and presence of autoantibodies, consistent with the small sample size (N = 76). In general, small studies are at risk of imbalance in prognostic factors, are associated with larger effect sizes, and should be considered in the context of these findings. Teplizumab was developed to delay the onset of stage 3 T1D in patients diagnosed with stage 2 T1D. Time to stage 3 T1D diagnosis was the primary efficacy end point in the TN-10 study. Longer time from randomization to disease progression is associated with delayed treatment with insulin and related short-term consequences. However, the clinical experts noted that it is currently uncertain whether the delayed onset of stage 3 T1D can be translated to longer-term clinical benefits, such as lower risk of macrovascular or microvascular events in patients with stage 3 T1D. It may also have an impact on patients' HRQoL during the disease-free period, in particular the psychosocial well-being of patients and their families; however, this was not examined in this study.

Based on feedback from the clinical experts consulted for this review, the eligibility criteria and baseline characteristics of patients randomized in the TN-10 study were somewhat different than those typically observed in clinical practice. For example, the proportion of patients older than 18 years may be larger in practice than in the TN-10 study. Also, nearly all patients in the study were white, which was inconsistent with what is seen in practice. As such, the patients enrolled in the study were unlikely to be representative of the racial and ethnic diversity of Canada. In addition, the trial used restricted exclusion criteria, while in clinical practice, a broader population might be eligible to receive treatment with teplizumab, including patients who may have abnormal blood counts or liver function tests; however, the clinical experts noted that the study findings can be generalized to the patient population in clinical practice.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the certainty of the evidence for outcomes considered most relevant to inform expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.

Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based

on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null. The threshold for a clinically important effect for time to stage 3 T1D in the study population was not obtained. Therefore, the target of the certainty of evidence assessment was the absence of any non-null effect for this end point. The thresholds for a clinically important effect for the change from baseline in levels of C-peptide, hemoglobin A1C, and the occurrence of harm events in the study population were also not obtained. Therefore, the target of certainty of the evidence assessment was the absence of any non-null effect for these end points.

[Table 1](#) presents the GRADE summary of findings for teplizumab versus placebo.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- time from randomization to stage 3 T1D diagnosis
- change from baseline in level of C-peptide
- change from baseline in level of hemoglobin A1C
- any SAEs
- AESIs.

Table 1: Summary of Findings for Teplizumab vs. Placebo for Patients With Stage 2 T1D

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Teplizumab	Difference		
Delay in onset of stage 3 T1D (ITT population)							
Time from randomization to stage 3 T1D, median months Median follow-up for teplizumab: 27.5 months Median follow-up for placebo: 17.8 months	76 (1 RCT)	NR	24.9 (9.5 to 48.6)	49.5 (32.2 to NE)	24.6 (NR)	Moderate ^a	Teplizumab likely results in an increase in time to onset of stage 3 T1D when compared with placebo. The clinical importance of the delay is uncertain.
Number of patients diagnosed with stage 3 T1D Median follow-up for teplizumab: 27.5 months Median follow-up for placebo: 17.8 months	76 (1 RCT)	NR	per 1,000 (NR)	per 1,000 (NR)	fewer per 1,000 (fewer to fewer per 1,000)	Moderate ^b	Teplizumab likely results in fewer patients progressing to stage 3 T1D when compared with placebo. The clinical importance of the decrease is uncertain.
Incidence of DKA							
NR; hence, the evidence is very uncertain about the effect of teplizumab on the incidence of DKA vs. any comparator.							
HRQoL							
Not assessed; hence, in the absence of comparative data, the evidence is very uncertain about the effect of teplizumab on HRQoL vs. any comparator.							
Harms (safety population)							
SAEs Median follow-up for teplizumab: 27.5 months Median follow-up for placebo: 17.8 months	76 (1 RCT)	NR	per 1,000 (NR)	per 1,000 (NR)	more per 1,000 (more to more per 1,000)	Low ^c	Teplizumab may result in an increase in the proportion of patients who experience SAEs when compared with placebo.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Teplizumab	Difference		
AESIs Median follow-up for teplizumab: 27.5 months Median follow-up for placebo: 17.8 months	76 (1 RCT)	NR		per 1,000 (NR)	more per 1,000 (NE to NE)	Low ^d	Teplizumab may result in an increase in the proportion of patients who experience AESIs when compared with placebo.

AESI = adverse event of special interest; CI = confidence interval; DCO = data cut-off; DKA = diabetic ketoacidosis; HR = hazard ratio; HRQoL = health-related quality of life; NE = not estimable; NR = not reported; RCT = randomized controlled trial; SAE = serious adverse event; T1D = type 1 diabetes; vs. = versus.

Notes: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

No adjustment for multiplicity was made in the analyses in the TN-10 study.

In the TN-10 study, the incidence of DKA was assessed as a harm outcome instead of an efficacy outcome. No DKA events had been reported at the DCO of November 30, 2018.

^aRated down 1 level for serious imprecision. There was no known threshold for a clinically important effect for the time to stage 3 T1D diagnosis. The sample size and/or number of events contributing to the analysis was small.

^bRated down 1 level for serious imprecision. There was no known threshold for a clinically important effect for the number of patients who progressed to stage 3 T1D. The sample size and/or number of events contributing to the analysis was small.

^cRated down 2 levels for very serious imprecision. No threshold of clinical importance could be established; therefore, the null was used. The point estimate suggests harm; however, the 95% CIs were wide and close to null, and therefore the effect of teplizumab on SAEs was uncertain.

^dRated down 2 levels for very serious imprecision. No threshold of clinical importance could be established; therefore, the null was used. The point estimate suggests harm; however, the 95% CIs were not estimable, and therefore the effect of teplizumab on AESIs was uncertain.

Sources: Clinical Study Report for the TN-10 trial; Sims et al. (2021); Lledó-Delgado et al. (2024); and additional information provided by the sponsor. Details included in the table are from the sponsor's Summary of Clinical Evidence.

Long-Term Extension Studies

Description of Studies

Participants who had not progressed to stage 3 T1D by the end of the TN-10 study (in June 2019) were transferred into the TN-01 study, and continued to be followed up and were included in the extended follow-up analyses of the primary end point, which was conducted after participants had been followed for a median duration of 80.46 months. Patients were informed of the treatment they received at the end of the TN-10 study and so were aware of treatment assignment in the long-term extension study. The results of median time from randomization to the diagnosis of stage 3 T1D, as well as metabolic outcomes, including measures of C-peptide response and glycemic control as measured by hemoglobin A1C levels, were reported.

Efficacy Results

At the median follow-up duration of 923 days from initial randomization, the proportion of patients who did not have stage 3 T1D was 50% (22 of 44 patients) in the teplizumab group and 22% (7 of 32 patients) in the placebo group. At the median follow-up duration of 80.46 months, the proportion of patients who did not have stage 3 T1D was 36% (16 of 44 patients) in the teplizumab group and 12.5% (4 of 32 patients) in the placebo group. Results of these extended follow-up analyses suggested that the treatment effect of teplizumab (delaying the onset of stage 3 T1D) was maintained during the longer follow-up in patients aged 8 years or older with a diagnosis of stage 2 T1D.

Harms Results

Harms outcomes were not assessed in the long-term extension studies.

Critical Appraisal

Longer-term efficacy and safety data of teplizumab were reported for a median follow-up duration of 80.46 months. Missing data handling was not reported during these periods. Time from randomization to stage 3 T1D and change in levels of C-peptide and hemoglobin A1C were reported. While these outcomes were objectively measured, the open-label observational design cannot control for the impact of patient behaviours or other treatments received during the extended follow-up period. Insufficient details of the efficacy outcomes were reported (e.g., between-group differences and associated 95% CIs were missing); therefore, a thorough evaluation of the long-term effect of teplizumab in the study population was not feasible. Harms outcomes were not examined in the extended follow-up analyses.

Additional Supportive Evidence

Rawshani et al. (2018)

In its reconsideration request, the sponsor provided a study by Rawshani and colleagues to support the value of delayed onset of T1D, especially in pediatric patients. The study explored the relationship between age at diagnosis of T1D and long-term clinical outcomes such as excess mortality and cardiovascular risk. The authors used data from 27,195 patients with T1D in a Swedish diabetes registry and 135,178 matched controls from the general population. Findings from this study suggested that children with T1D (< 10 years of age) had 4.1 times the risk of death compared to the general population, which was associated with a life expectancy that was approximately 14 to 18 years shorter. Patients who developed T1D as young adults

(between 26 and 30 years of age) had 2.8 times the risk of death compared to the general population, which was associated with a life expectancy that was approximately 10 years shorter. In addition, the study suggested that younger age at onset of stage 3 T1D was associated with higher hemoglobin A1C levels and impaired kidney function earlier in the disease course, as well as an increased risk of cardiovascular disease. This study, however, presented with the common limitations associated with nonrandomized studies, of which the confounding lifestyle factors were particularly important in the case of diabetes complications. Individuals recruited in this study were patients from the general population who had already received a diagnosis of stage 3 T1D.

Testing Procedure Considerations

Testing for diabetes-related autoantibodies is not part of the current standard care for identifying individuals with early-stage T1D (including stage 2), and access to autoantibody testing varies by jurisdiction. While dysglycemia testing is widely available and publicly funded, the availability, reimbursement status, and access to autoantibody testing varies by jurisdiction. This could be a barrier to implementation and may result in inequitable access to teplizumab if it were to be funded. Identification of populations eligible for testing remains a key challenge.

Ethical Considerations

Patient group, clinician group, and drug plan input was reviewed, in addition to consultation with clinical experts, to identify ethical considerations regarding the use of teplizumab to delay the onset of stage 3 T1D in adults and pediatric patients aged 8 years or older with stage 2 T1D.

Diagnosis, Treatment, and Experiences of People Living With Stage 2 T1D

- Rates of progression from stage 2 to stage 3 T1D are variable and suggest that stage 2 is not a uniform risk category. Factors like age and autoantibody combinations may affect this trajectory, complicating decisions about treatment eligibility and raising concerns about how risk is communicated.
- In Canada, screening for T1D-associated autoantibodies is largely limited to research contexts and individuals with a family history of T1D, despite most new diagnoses occurring in those without such history. This limited access constrains early identification and raises questions of fairness, and has the potential to reinforce existing inequities in T1D care, especially in the context of prospective early interventions like teplizumab.
- In the absence of early diagnosis (e.g., at stage 2 or earlier), people with T1D and their caregivers described experiencing the diagnosis of T1D as abrupt as well as emotionally and logistically overwhelming. Patient group input indicated that even a modest delay in disease progression would be valuable, as it could offer people with T1D and their caregivers time to prepare for the daily demands of diabetes management.

- Beyond the absence of approved therapies, significant unmet needs remain in early-stage T1D, including gaps in identification, education, and access to care. Without systematic screening, many people remain undiagnosed until serious complications occur, underscoring broader systemic challenges in delivering equitable care.

Clinical Evidence Used in the Evaluation of Teplizumab

- A phase II trial (the TN-10 trial) demonstrated a statistically significant delay (median of approximately 2 years) in progression from stage 2 to stage 3 T1D in the active arm when compared to placebo. While clinical experts viewed this delay as clinically meaningful, long-term safety and efficacy remain uncertain. The trial did not evaluate outcomes such as glycemic control after diagnosis or effects on long-term complications, leaving important gaps in understanding the broader value of treatment.
- Several ethical considerations complicate interpretation of the trial evidence:
 - **Limited participant diversity:** All participants in the active treatment arm (100%) and nearly all participants in the placebo arm (93.8%) were white. Clinical experts suggested that this is more reflective of the demographics seen in opt-in, family-based screening programs rather than the actual population with T1D. This raises questions about whether findings can be confidently extended to racialized populations or those less represented in early-stage T1D, particularly in the context of known disparities in T1D diagnosis, management, and outcomes across racial and socioeconomic lines.
 - **Restricted inclusion criteria:** Only individuals with a family history of stage 3 T1D were eligible for enrolment. This is particularly problematic given that the majority of people who develop T1D do not have a family history, and that progression rates do not appear to differ based on family history once stage 2 is identified. This impacts the generalizability of benefit observed in the trial for the approximately 85% of the patient population who eventually develop T1D with no family history, and it raises ethical considerations about equitable access to screening, diagnosis, care, and potentially reimbursement for those patients.
 - **Uncertain value of delay:** The primary outcome was time to stage 3 diagnosis, and while the trial demonstrated an average delay in progression of approximately 2 years, the long-term significance of this outcome remains unclear. There is no evidence that delay alters the course of long-term complications, and patient reported outcomes (such as HRQoL) were not assessed. As such, the clinical and experiential value of delayed progression remains difficult to interpret.

Clinical Use of Teplizumab

- Teplizumab is positioned as a first-in-class immunotherapy for delaying the onset of symptomatic T1D (stage 3). Clinical experts and patient group input were broadly optimistic about its potential, viewing it as a meaningful step forward in a treatment landscape where no disease-modifying therapies currently exist for T1D at any stage.
- The perceived experiential value of delay is not consistently reflected in lived experience. While the idea of delaying stage 3 is broadly appealing, early survey evidence suggests that the emotional

or psychosocial benefit may be limited. Most patients and caregivers reported ongoing anxiety and vigilance after treatment, with few describing meaningful emotional relief.

- Although teplizumab's safety profile was considered manageable, long-term effects remain unclear. AEs were generally mild but must be weighed against the lack of evidence for long-term clinical benefit or improved psychosocial outcomes. These uncertainties are particularly important given the pediatric use of the therapy, raising questions about proportionality, risk exposure, and the potential for unnecessary medicalization.
- If teplizumab is publicly reimbursed, decisions about access will be complicated by both scientific uncertainty and current limitations in screening. Not all individuals with stage 2 T1D carry the same short-term risk of progression, yet tools to guide prioritization are lacking, potentially introducing new inequities. Moreover, those currently diagnosed with stage 2 are disproportionately drawn from screened populations with a family history of T1D.
- Access to teplizumab will also depend on the availability of specialist care and infusion infrastructure. People living in rural or remote areas may face particular barriers due to travel demands and uneven access to endocrinologists and infusion services.
- The approved indication for teplizumab may not align with emerging clinical demand, raising concerns about off-label use and provider burden. Some families may seek access for children younger than 8 years or for individuals newly diagnosed with stage 3. Experts expressed concern that such pressure — particularly in pediatric settings that might be emotionally charged — may lead to moral distress, complicating clinical decisions where evidence is still limited and trust is critical.

Health Systems Impact

- Successfully implementing teplizumab will depend not only on clinical outcomes but also on the health systems' readiness to deliver screening, diagnosis, treatment, and follow-up in an equitable and coordinated way. Canada currently lacks a population-level screening program for T1D, and those diagnosed with stage 2 T1D are typically identified through family-based screening. Expanding access would require substantial infrastructure. Without coordinated systems, individuals may face fragmented or inconsistent care depending on their location.
- The 14-day IV infusion schedule for teplizumab also presents logistical challenges. While some infusion services are publicly available, many rely on private infrastructure, which may limit access for those in rural or underserved areas. Caregiver burden is a particular concern for pediatric patients, as treatment involves time off work, travel, and ongoing monitoring during a presymptomatic stage. Postinfusion support could further strain specialist services in areas with limited clinical capacity.
- Given uncertainty about whether delayed progression improves long-term outcomes or quality of life, some have argued that public resources might be better spent on proven supports (such as diabetes education, insulin pumps, or continuous glucose monitors) that directly improve health for individuals already living with stage 3 T1D. Balancing investment in emerging therapies with established interventions remains an important consideration for funding decisions.

Economic Evidence

Cost and Cost-Effectiveness

- Teplizumab is available as a sterile solution for IV infusion (1 mg/mL). At the submitted price of \$18,410.00 per 2 mL vial, the cost of teplizumab is expected to be \$257,740 per patient for a single course of treatment, based on the Health Canada–recommended dosage.
- Clinical efficacy in the economic analysis was derived from the TN-10 trial, which compared teplizumab with placebo in adult and pediatric patients aged 8 years or older with stage 2 T1D (i.e., individuals who tested positive for 2 or more diabetes-related autoantibodies identified by screening). Evidence submitted by the sponsor indicated that teplizumab is likely to increase the time to onset of stage 3 T1D (i.e., manifestation of typical clinical symptoms and signs of T1D) compared to placebo among adult and pediatric patients aged 8 years or older with stage 2 T1D. No evidence was provided suggesting that teplizumab is curative (i.e., would prevent an individual with stage 2 T1D from reaching stage 3 T1D). As noted in the Clinical Review report, the clinical importance of the delay in onset is highly uncertain.
- The results of the CDA-AMC base case suggest the following:
 - Teplizumab will be associated with higher costs to the health care systems than no intervention (incremental costs = \$221,630), primarily driven by increased costs associated with drug acquisition, partly offset by disease management of stage 3 T1D.
 - Teplizumab is predicted to be associated with a gain of 0.24 life-years compared to no intervention. When the impact on HRQoL is also considered, teplizumab is predicted to result in a gain of 0.31 quality-adjusted life-years (QALYs) compared to no intervention, from the health care payer perspective. When caregiver benefits are considered in the societal perspective, the incremental benefit is increased (incremental benefit = 0.36 QALYs).
 - The incremental cost-effectiveness ratio (ICER) of teplizumab compared to no intervention was \$747,542 per QALY gained in the CDA-AMC base case from the publicly funded health care payer perspective, and \$608,736 per QALY gained from the societal perspective. The estimated ICER was highly sensitive to the parametric distribution used to estimate the proportion of patients at risk of developing stage 3 T1D. This finding is associated with significant uncertainty as the long-term benefit associated with teplizumab is unknown.
- Although the CDA-AMC base case estimated a gain in QALYs with teplizumab compared to no intervention (incremental benefit = 0.30 QALYs), approximately 90% of the incremental benefit was gained in the extrapolated period (i.e., after a median 24.5 months of follow-up). In the absence of long-term evidence, the incremental QALYs for teplizumab predicted in the CDA-AMC base case are highly uncertain and may be overestimated. Additionally, health care resource use for stage 3 T1D is associated with significant uncertainty, as the mixed regression model used to estimate health care resource use costs does not reflect clinical expectations or published literature from Canada. Additional price reductions may therefore be required.

- CDA-AMC estimates that the budget impact of reimbursing teplizumab for the indicated population will be approximately \$485 million over the first 3 years of reimbursement compared to the amount currently spent on no intervention, which reflects the predicted expenditure over this period. The actual budget impact of reimbursing teplizumab will depend on the number of people eligible and identified for treatment, and the uptake of teplizumab. The economic feasibility of adoption must be addressed, given that the predicted incremental budget impact of reimbursing teplizumab is predicted to be greater than \$40 million in year 2 and year 3, in addition to the magnitude of uncertainty in the estimated budget impact.
- Screening is a significant factor that was not adequately considered in the economic evaluation or budget impact analysis. While a targeted screening approach focusing on potential patients with a family history may be most feasible, clinical expert input indicated that this would only identify 15% to 20% of patients with stage 2 T1D who could benefit from teplizumab. The potential benefits of a screening program should not be understated, as DKA often occurs in undiagnosed patients and patient-relevant outcomes may be improved from a screening program itself. The budget impact considers a targeted approach where █████% of first-degree and second-degree relatives are motivated to receive autoantibody testing; however, this can only capture the approximately 15% of patients with T1D who have a family history. Depending on the screening approach, the budget impact may be substantially underestimated.

Request for Reconsideration

The sponsor filed a request for reconsideration of the draft recommendation for teplizumab to delay the onset of stage 3 T1D in adult and pediatric patients aged 8 years or older with stage 2 T1D. In their request, the sponsor identified the following issues:

- The sponsor expressed concerns regarding the committee's interpretation of the findings, especially that the submitted evidence was deemed insufficient at this time to support a positive recommendation.
- According to the sponsor, patients included in the studies were representative of those seen in clinical practice in Canada, especially regarding family history and ethnicity.
- The sponsor also argued that the delay in progression is suggestive of clinically meaningful effectiveness.
- Finally, the sponsor highlighted that identifying suitable candidates for teplizumab therapy could be done in the absence of a population-level screening program for stage 2 T1D.

In the meeting to discuss the sponsor's request for reconsideration, CDEC considered the following information:

- information from the initial submission related to the issues identified by the sponsor
- feedback from 2 clinical specialists with expertise in diagnosing and treating patients with T1D

- feedback on the draft recommendation from 2 patient groups: Breakthrough T1D Canada and Diabetes Canada
- feedback on the draft recommendation from 4 clinicians or clinician groups: BC Diabetes, clinicians from various institutions, Durham Care Clinic Group, and the University of Alberta and Kaye Edmonton Diabetes Clinic
- feedback on the draft recommendation from the public drug plans that participate in the reimbursement review process.

All feedback received in response to the draft recommendation is available on the CDA-AMC website.

CDEC Information

Members of the Committee

Dr. Peter Jamieson (Chair), Dr. Kerry Mansell (Vice-Chair), Dr. Sally Bean, Daryl Bell, Dan Dunskey, Dr. Ran Goldman, Dr. Trudy Huyghebaert, Morris Joseph, Dr. Dennis Ko, Dr. Christine Leong, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Dr. Edward Xie, and Dr. Peter Zed

Initial meeting date: July 23, 2025

Regrets: Two expert committee members did not attend.

Conflicts of interest: None

Members of the Committee

Dr. Peter Jamieson (Chair), Dr. Kerry Mansell (Vice-Chair), Sally Bean, Daryl Bell, Dan Dunskey, Dr. Ran Goldman, Dr. Trudy Huyghebaert, Dr. Dennis Ko, Dr. Christine Leong, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Carla Velastegui, Dr. Edward Xie, and Dr. Peter Zed

Reconsideration meeting date: November 26, 2025

Regrets: Two expert committee members did not attend.

Conflicts of interest: None



Canada's Drug Agency
L'Agence des médicaments du Canada
Drugs. Health Technologies and Systems. Médicaments, technologies de la santé et systèmes.

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