Blue Cross Blue Shield Blue Care Network of Michigan

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P&T Date: 02/13/2025

Tzield™ (teplizumab-mzwv)

HCPCS: J9381

Policy:

Requests must be supported by submission of chart notes and patient specific documentation.

A. Coverage of the requested drug is provided when all the following are met:
   a. Patient has Stage 2 type 1 diabetes confirmed by the following:
      i. Documentation of the presence of at least two of the following pancreatic islet autoantibodies:
         a) Glutamic acid decarboxylase 65 (GAD65) autoantibody
         b) Insulin autoantibody (IAA)
         c) Insulinoma-associated antigen 2 autoantibody (IA-2A)
         d) Zinc transporter 8 autoantibody (ZnT8A)
         e) Islet cell autoantibody (ICA)
      ii. Documentation of dysglycemia without overt hyperglycemia as demonstrated by at least ONE of the following results on an oral glucose tolerance test (OGTT). If an OGTT is not available, an alternative method for diagnosis of dysglycemia without overt hyperglycemia may be appropriate:
         a) Fasting blood glucose level of 100 to <126 mg/dL
         b) 2-hour post-prandial glucose of 140 to <200 mg/dL
         c) Postprandial glucose level at 30, 60, or 90 minutes $\geq$ 200 mg/dL
   b. Clinical history of patient does not suggest presence of type 2 diabetes
   c. FDA approved age
   d. Prescribed by or in consultation with an endocrinologist
   e. Trial and failure, contraindication, OR intolerance to the preferred drugs as listed in BCBSM/BCN's utilization management medical drug list.

B. Quantity Limitations, Authorization Period and Renewal Criteria
   a. Quantity Limits: Align with FDA recommended dosing
   b. Authorization Period: 60 days
   c. Renewal Criteria: Not applicable as no further authorization will be provided

***Note: Coverage and approval duration may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at http://www.cms.hhs.gov/. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

Background Information:

- Type 1 diabetes (T1D) is an autoimmune disorder in which the pancreas is unable to produce enough insulin due to autoimmune destruction of pancreatic beta cells. The CDC estimates that about 5-10% of the diabetic population has T1D which typically develops in children, teenagers, and young adults; however, T1D can happen at any age. Markers of immune destruction of the beta cell include islet cell autoantibodies, autoantibodies to insulin, autoantibodies to GAD65, and autoantibodies to tyrosine phosphatases I-2 and IA-2B. At least one, and usually more, of these autoantibodies are present in 85-90% of individuals when fasting hyperglycemia is first detected.

- In T1D the rate of beta cell destruction is variable and the patient may go through distinct stages before progressing to symptomatic disease requiring insulin. According to the American Diabetes Association's (ADA) Standards of Medical Care in Diabetes (2025), there are three distinct stages of T1D.

    - Stage 1 is characterized by autoimmunity, normoglycemia, and is pre-symptomatic. Multiple (at least two) islet autoantibodies are typically present and the patient exhibits no evidence of impaired glucose tolerance (IGT) or impaired fasting glucose (IFG). 5-year risk of developing symptomatic T1D is about 44% overall but varies depending on a number of factors.

    - Stage 2 exhibits autoimmunity, dysglycemia (i.e., abnormal glucose tolerance), and is also pre-symptomatic. In this stage, islet autoantibodies are present (usually multiple) and dysglycemia is demonstrated by IFG (i.e., fasting plasma glucose of 100-125 mg/dL) and/or IGT (i.e., 2-hour plasma glucose of 140-199 mg/dL on oral OGTT). A hemoglobin A1c of 5.7-6.4% or $\geq$ 10% increase in A1c may also be diagnostic of this stage. At stage 2, there is an approximately 60% risk of developing a clinical diagnosis of T1D by 2 years and approximately 75% risk within 5 years.

    - Stage 3 is also characterized by autoimmunity, but at this point the patient has progressed to overt hyperglycemia and is symptomatic. Autoantibodies may become absent at this stage and the patient can be diagnosed with T1D by standard criteria outlined in the ADA's Standards of Medical Care.

- The presence of IFG as defined in Stage 2 and/or IGT as defined in Stage 2 and/or an A1c of 5.7-6.4% define prediabetes, a term for those whose glucose levels do not meet criteria for diabetes yet demonstrate abnormal carbohydrate metabolism. Patients with prediabetes are at relatively high risk for future development of diabetes. The 2025 ADA Standards of Medical Care recommend fasting plasma glucose, 2-hour plasma glucose during a 75-gram OGTT, and A1c as equally appropriate for screening for prediabetes. When using OGTT as a screening tool, adequate carbohydrate intake of at least 150 grams per day should be assured prior to testing; fasting and carbohydrate restriction can falsely elevate glucose level with an oral glucose challenge.

- The 2025 ADA Standards of Medical Care recommend screening for pre-symptomatic T1D using screening tests to detect autoantibodies to insulin, GAD, islet antigen 2, or ZnT8 as an option for first-degree family members of a proband with T1D. The development and persistence of multiple islet autoantibodies is considered a risk factor for clinical diabetes and may serve as an indication for screening for Stage 2 T1D.

- Delay of development of overt diabetes in patients with Stage 2 T1D has been a promising avenue of research. The FDA approved Tzield (teplizumab), an anti-CD3 antibody, to delay the onset of Stage 3 T1D in adults and pediatric patients 8 years of age and older with Stage 2 T1D. Tzield is the first and only FDA-approved pharmacologic therapy

for delaying the onset of clinical diabetes and continues to be investigated for the treatment of newly diagnosed type 1 diabetics. The 2025 ADA Standards of Medical Care recommends that Tzield, to delay the onset of symptomatic T1D (stage 3), should be considered in selected individuals 8 years of age and older with stage 2 T1D, and management should be in a specialized setting with appropriately trained personnel.

- According to the prescribing information, eligibility for treatment requires that the patient's clinical history does not suggest type 2 diabetes (T2D) and that Stage 2 T1D be confirmed by documentation of the following:
    - At least 2 positive pancreatic islet cell autoantibodies.
    - Dysglycemia without overt hyperglycemia using an OGTT. If an OGTT is not available, an alternative method for diagnosing dysglycemia without overt hyperglycemia may be appropriate.
- Alternative methods for diagnosing dysglycemia does not suggest a specific or defined test, but rather alternative means of establishing the blood glucose levels indicative of dysglycemia. This could be accomplished with a fasting blood glucose draw, any blood draw measuring glucose with levels over 200 mg/dL, or blood sugar levels in response to a mixed meal prep or an alternative to the Glucola used in the OGTT at 2 hours.
- Tzield was evaluated in the pivotal Phase II, randomized, double-blind, placebo-controlled "At-Risk" TN-10 trial in patients 8 to 49 years of age who had a direct relative with T1D and were considered high risk for development of clinical diabetes (n=76).
    - All patients were classified as having Stage 2 T1D defined by both of the following:
        - The presence of two or more diabetes-related pancreatic islet autoantibodies (GAD65, IAA, IA-2A, ZnT8A, or ICA)
        - Evidence of dysglycemia on OGTT, defined as any of the following occurring at least once (patients < 18 years) or on two occasions (patients > 18 years):
            - Fasting blood glucose level of 110mg/dL to < 126 mg/dL, OR
            - 2-hour postprandial glucose > 140 mg/dL and < 200 mg/dL, OR
            - Postprandial glucose level at 30, 60, or 90 minutes $\geq$ 200 mg/dL
    - Eligible patients with a first-degree relative (parent, sibling, offspring) were required to be between 8 and 45 years old, while those with a second- or third-degree relative (niece, nephew, aunt, uncle, cousin, grandchild) were between 8 and 20 years old.
    - The primary endpoint of Study TN-10 was the elapsed time from randomization to development of Stage 3 T1D diagnosis.
    - Stage 3 T1D was diagnosed in 20 (45%) of the Tzield-treated patients and in 23 (72%) of the placebo-treated patients. The median time from randomization to Stage 3 T1D diagnosis was 50 months for the Tzield arm and 25 months for the placebo arm. This represents a statistically significant delay in the development of Stage 3 T1D by about 2 years (p=0.0066).
    - A published follow-up of the TN-10 trial reported that those in the Tzield arm had a median time to diagnosis of 59.6 months compared to 27.1 months for those in the placebo arm (p=0.01), extending the median delay

in diagnosis of Stage 3 T1D with Tzield to 2.7 years. Note that this data was not reviewed by the FDA in the approval of Tzield.

- Tzield is administered intravenously once daily for 14 consecutive days. Based on the available literature, additional Tzield treatments are not recommended to delay the onset of clinical T1D in at-risk individuals.

References:

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2. Herold KC, et al. An anti-CD3 antibody, teplizumab, in relatives at risk for type 1 diabetes [published correction appears in N Engl J Med. 2020 Feb 6;382(6):586]. N Engl J Med. 2019;381(7):603-613. doi:10.1056/NEJMoa1902226
3. Manufacturer Press Release. Provention Bio's Teplizumab Continued to Significantly Delay the Onset of Insulin-Dependent Type 1 Diabetes (T1D) in Presymptomatic Patients. June 15, 2020. Accessed on June 27, 2022. Available at: https://investors.proventionbio.com/2020-06-15-Provention-Bios-Teplizumab-Continued-to-Significantly-Delay-the-Onset-of-Insulin-Dependent-Type-1-Diabetes-T1D-in-Presymptomatic-Patients
4. IPD Analytics. Teplizumab New Drug Preview. August 5, 2022. Accessed August 31, 2022. https://www.ipdanalytics.com
5. American Diabetes Association Professional Practice Committee; 2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes—2025. Diabetes Care 1 January 2025; 48 (Supplement_1): S27–S49. https://doi.org/10.2337/dc25-S002
6. American Diabetes Association Professional Practice Committee; 3. Prevention or Delay of Diabetes and Associated Comorbidities: Standards of Care in Diabetes—2025. Diabetes Care 1 January 2025; 48 (Supplement_1): S50–S58. https://doi.org/10.2337/dc25-S003
7. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2014;37(Suppl. 1):S81–S90
8. Manufacturer press release. TZIELD™ (teplizumab-mzwv) approved by FDA as the first and only treatment indicated to delay the onset of Stage 3 type 1 diabetes (T1D) in adult and pediatric patients aged 8 years and older with Stage 2 T1D. November 17, 2022. Accessed on November 18, 2022. Available at: https://investors.proventionbio.com/2022-11-17-TZIELD-TM-teplizumab-mzwv-approved-by-FDA-as-the-first-and-only-treatment-indicated-to-delay-the-onset-of-Stage-3-type-1-diabetes-T1D-in-adult-and-pediatric-patients-aged-8-years-and-older-with-Stage-2-T1D.
9. Tzield (teplizumab-mzwv) [prescribing information]. Provention Bio, Inc. Red Bank, NJ; November 2022.

<table>
<tr><th colspan="3">Policy History</th></tr>
<tr><th>#</th><th>Date</th><th>Change Description</th></tr>
<tr><td>1.5</td><td>Effective Date: 02/13/2025</td><td>Changed the fasting plasma glucose criteria requirement from 110 mg/dL to 100 mg/dL and postprandial glucose from > 200 mg/dL to ≥ 200 mg/dL to align with ADA Standards of Care (2025)</td></tr>
<tr><td>1.4</td><td>Effective Date: 02/08/2024</td><td>Annual review of criteria performed, no changes were made</td></tr>
<tr><td>1.3</td><td>Effective Date: 02/02/2023</td><td>New policy - this criteria replaces previously approved preliminary criteria</td></tr>
<tr><td>1.2</td><td>Effective Date: 12/22/2022</td><td>UM medical management system update for BCBS and BCN
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<tr><th>Line of Business</th><th>PA Required in Medical Management System (Yes/No)</th></tr>
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<tr><td>MAPPO</td><td>Yes</td></tr>
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<tr><td>1.0</td><td>Effective Date: 10/06/2022</td><td>Preliminary drug review</td></tr>
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** The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or http://dailymed.nlm.nih.gov/dailymed/index.cfm*