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Reviewed: 01/08/25

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Subject: Teplizumab (Tzield™) Injection

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DESCRIPTION:

Teplizumab is a CD3-directed monoclonal antibody FDA-approved in November 2022 to delay the onset of stage 3 type 1 diabetes in adult and pediatric patients 8 years and older with stage 2 type 1 diabetes. The mechanism of benefit may involve partial agonistic signaling and deactivation of pancreatic beta cell autoreactive T lymphocytes. Teplizumab leads to an increase in the proportion of regulatory T cells and of exhausted CD8+ T cells in peripheral blood. Type 1 diabetes is an autoimmune condition in which the pancreas does not produce enough insulin. According to the Centers for Disease Control and Prevention (CDC), about 5 to 10% of people with diabetes have type 1. It is one of the most common chronic diseases in childhood, with 45% of all cases presenting before 10 years of age. According to the Juvenile Diabetes Research Foundation, there are approximately 1.6 million Americans living with type 1 diabetes today, of whom 200,000 are less than 20 years of age, and 64,000 additional people are diagnosed annually. Patients who have a genetic susceptibility to developing type 1 diabetes progress through stages before developing overt hyperglycemia requiring insulin treatment. Stage 1 is defined by the appearance of autoantibodies. Stage 2 involves dysglycemia. At Stage 3, autoimmune destruction of beta cells has occurred, so blood glucose is elevated, and patients are symptomatic and require insulin treatment. The development of autoantibodies may occur months to years before the onset of clinical symptoms. The American Diabetes Association (ADA) recommends screening for autoantibodies in patients with a family history of type 1 diabetes or otherwise known elevated genetic risk. The ADA's Standard of Care in Diabetes - 2025 (Section 3. Prevention or Delay of Diabetes and Associated Comorbidities), includes the following grade B recommendation regarding pharmacologic interventions for type 1 diabetes, "3.15 Teplizumab-mzwv infusion to delay the onset of symptomatic type 1 diabetes should be discussed with selected individuals aged ≥8 years with stage 2 type 1 diabetes. Management should be in a setting with appropriately trained personnel." The peak age of type 1 diabetes diagnosis is 13 to 14 years, but people can be diagnosed much younger or older. Currently, broad-population screening for type 1 diabetes does not occur. Interventions at Stage 1 or Stage 2 may delay the

progression to Stage 3 and life-long insulin dependence. Provention Bio estimates that up to 200,000 people in the United States have two or more diabetes-related autoantibodies and dysglycemia. Of this group, 30,000 patients are familial direct relatives of patients with T1D.

The safety and effectiveness of teplizumab leading to its initial FDA approval was assessed in a randomized, double-blind, event-driven, placebo-controlled study (Study TN-10; NCT01030861) in 76 patients (8 to 49 years of age) with Stage 2 type 1 diabetes. Stage 2 type 1 diabetes was defined as having both of the following: (1) two or more of the following pancreatic islet autoantibodies: (a) Glutamic acid decarboxylase 65 (GAD) autoantibodies, (b) Insulin autoantibody (IAA), (c) Insulinoma-associated antigen 2 autoantibody (IA-2A), (d) Zinc transporter 8 autoantibody (ZnT8A), and (e) islet cell autoantibody (ICA); and (2) dysglycemia on oral glucose tolerance testing. Patients were randomized to receive teplizumab or placebo once daily by intravenous (IV) infusion for 14 days. Patients in the teplizumab group had a total drug exposure that was comparable to the total drug exposure achieved with the recommended total teplizumab dosage in the product labeling. The primary efficacy endpoint in this study was the time from randomization to development of Stage 3 type 1 diabetes diagnosis. In this study, 45% were female; 97% White, and 95% were from the United States. The median age was 14 years (72% were less than 18 years old). Stage 3 type 1 diabetes was diagnosed in 20 (45%) of the teplizumab-treated patients and in 23 (72%) of the placebo-treated patients. A Cox proportional hazards model, stratified by age and oral glucose tolerance test status at randomization, demonstrated that the median time from randomization to Stage 3 type 1 diabetes diagnosis was 50 months in the teplizumab group and 25 months in the placebo group, for a difference of 25 months. With a median follow-up time of 51 months, therapy with teplizumab resulted in a statistically significant delay in the development of Stage 3 type 1 diabetes, hazard ratio 0.41 (95% CI: 0.22 to 0.78; p=0.0066). The study was not designed to assess whether there were differences in the effectiveness between subgroups based on demographic characteristics or baseline disease characteristics.

POSITION STATEMENT:

The administration of teplizumab (Tzield) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "6"):

1. Member has a diagnosis of Stage 2 type 1 diabetes as confirmed by **BOTH** of the following ("a" and "b") - *medical record documentation of the autoantibodies tests (at least two separate dates) and labs confirming dysglycemia must be submitted*:
    a. Presence of **TWO or more** of the following pancreatic islet cell autoantibodies assessed in the past 6 months on at least **TWO** separate occasions:
        - Glutamic acid decarboxylase 65 (GAD) autoantibodies
        - Insulin autoantibody (IAA)
        - Insulinoma-associated antigen 2 autoantibody (IA-2A)
        - Zinc transporter 8 autoantibody (ZnT8A)
        - Islet cell autoantibody (ICA)
    b. Dysglycemia without overt hyperglycemia defined as **ANY** of the following assessed in the past 90 days:

- A 2-hour postprandial plasma glucose level, following an oral glucose tolerance test, of **at least** 140 mg/dL (7.8 mmol/L) but **less than** 200 mg/dL (11.1 mmol/L)
- Fasting plasma glucose level of **at least** 100 mg/dL (5.6 mmol/L) but **less than** 126 mg/dL (7 mmol/L)
- Hemoglobin A1C (HbA1C) of **at least** 5.7% (39 mmol/mol) [or greater than or equal to a 10% increase compared to baseline], but **less than** 6.5% (48 mmol/mol)

2. Member does **NOT** have **ANY** of the following:
    a. Clinical history consistent with type 2 diabetes
    b. Stage 3 type 1 diabetes (e.g., presence of overt hyperglycemia such as a 2-hour postprandial plasma glucose level of ≥200 mg/dL, fasting plasma glucose level of ≥126 mg/dL, HbA1C ≥6.5%, or insulin dependence)
    c. Lymphocyte count less than 1,000 lymphocytes/mcL
    d. Hemoglobin less than 10 g/dL
    e. Platelet count less than 150,000 platelets/mcL
    f. Absolute neutrophil count (ANC) less than 1,500 neutrophils/mcL
    g. Elevated ALT or AST greater than 2-times the upper limit of normal (ULN) or bilirubin greater than 1.5 times ULN
    h. Laboratory or clinical evidence of acute infection with Epstein-Barr virus (EBV) or cytomegalovirus (CMV)
    i. Active serious infection or chronic active infection other than localized skin infections
3. Teplizumab is prescribed by, or in consultation with, an endocrinologist
4. Member is at least 8 years of age or older
5. Member has **NOT** previously received treatment with teplizumab in their lifetime
6. The daily dosage of teplizumab does not exceed the following for a total of 14 doses, and must be achieved using the fewest number of vials possible:
    - Day 0: 65 mcg/m^2
    - Day 1: 125 mcg/m^2
    - Day 2: 250 mcg/m^2
    - Day 3: 500 mcg/m^2
    - Days 4 through 13: 1,030 mcg/m^2

Approval duration: 1 month (to allow a single 14-day course of treatment)

DOSAGE/ADMINISTRATION:

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FDA-approved

- Indicated to delay the onset of Stage 3 type 1 diabetes in adults and pediatric patients 8 years of age and older with Stage 2 type 1 diabetes
- Confirm Stage 2 type 1 diabetes by documenting:
  - At least two positive pancreatic islet cell autoantibodies
  - Dysglycemia without overt hyperglycemia using an oral glucose tolerance test (if an oral glucose tolerance test is not available, an alternative method for diagnosing dysglycemia without overt hyperglycemia may be appropriate)
- Ensure the clinical history of the patient does not suggest type 2 diabetes.
- Prior to initiating teplizumab, obtain a complete blood count and liver enzyme tests. Use is not recommended in patients with:
  - Lymphocyte count less than 1,000 lymphocytes/mcL
  - Hemoglobin less than 10 g/dL
  - Platelet count less than 150,000 platelets/mcL
  - Absolute neutrophil count less than 1,500 neutrophils/mcL
  - Elevated ALT or AST greater than 2 times the upper limit of normal (ULN) or bilirubin greater than 1.5 times ULN
  - Laboratory or clinical evidence of acute infection with Epstein-Barr virus (EBV) or cytomegalovirus (CMV)
  - Active serious infection or chronic active infection other than localized skin infections
- Administer all age-appropriate vaccinations prior to starting teplizumab:
  - Administer live-attenuated (live) vaccines at least 8 weeks prior to treatment
  - Administer inactivated (killed) vaccines or mRNA vaccines at least 2 weeks prior to treatment
- Administer teplizumab by intravenous (IV) infusion (over a minimum of 30 minutes), using a body surface area (BSA)-based dosing, once daily for 14 consecutive days as follows:
  - Day 1: 65 mcg/m^2
  - Day 2: 125 mcg/m^2
  - Day 3: 250 mcg/m^2
  - Day 4: 500 mcg/m^2
  - Days 5 through 14: 1,030 mcg/m^2
- Do not administer two doses on the same day.

Dose Adjustments

- Hepatic Impairment - Specific guidelines for dosage adjustments in hepatic impairment are not available; it appears that no dosage adjustments are needed. Teplizumab therapy is not recommended in patients with hepatic disease whose alanine aminotransferase (ALT) or aspartate aminotransferase (AST) concentrations are greater than 2 times the upper limit of normal (ULN) or bilirubin concentration is greater than 1.5 times the ULN
- Renal Impairment - Specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed.

Drug Availability

- Clear and colorless solution [2 mg/2 mL (1 mg/mL)] supplied in a single-dose vial as follows:
  - Carton of 1 single dose vial - NDC 73650-316-01
  - Carton of 10 single dose vials - NDC 73650-316-10
  - Carton of 14 single dose vials - NDC 73650-316-14
- Refrigerate vials at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Store upright. Do not freeze or shake the vials.

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- None

Precautions/Warnings

- **Cytokine Release Syndrome (CRS)**: Premedicate, monitor liver enzymes, discontinue in those that develop elevated ALT or AST more than 5 times the upper limit of normal, and if severe CRS develops consider temporarily pausing dosing.
- **Serious Infections**: Use of teplizumab is not recommended in patients with active serious infection or chronic infection. Monitor for signs and symptoms of infection during and after teplizumab treatment. If a serious infection develops, discontinue teplizumab.
- **Lymphopenia**: Monitor white blood cell counts during the treatment period. If prolonged severe lymphopenia (<500 cells per mcL lasting 1 week or longer) develops, discontinue teplizumab.
- **Hypersensitivity Reactions**: If severe hypersensitivity reactions occur, discontinue Tzield and treat promptly.
- **Vaccinations**: Administer all age-appropriate vaccinations prior to starting teplizumab. See recommendations regarding live-attenuated, inactivated, and mRNA vaccines.

BILLING/CODING INFORMATION:

HCPCS Coding

J9381	Injection, teplizumab-mzwv, 5 mcg

ICD-10 Diagnosis Codes That Support Medical Necessity

E10.A2	Type 1 diabetes mellitus, presymptomatic, Stage 2

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

None

RELATED GUIDELINES:

None

OTHER:

None

REFERENCES:

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11. Tzield (teplizumab-mzwv injection) [package insert]. Provention Bio, Inc. Red Bank, NJ. December 2023.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 01/08/25.

GUIDELINE UPDATE INFORMATION:

02/15/23	New Medical Coverage Guideline.
04/01/23	Revision: Added HCPCS code C9149.
07/01/23	Revision: Added HCPCS code J9381 and deleted codes C9149 and J3590.
11/15/23	Revision to guideline consisting of updating the Position Statement including the criteria for defining dysglycemia and the specialist prescribing requirement.
02/15/24	Review and revision to guideline consisting of updating the description and references.
10/01/24	Revision: Added ICD-10 code E10.A2 and deleted codes E10.8 and E10.9.
02/15/25	Review and revision to guideline consisting of updating the description, position statement, and references. Added requirements that pancreatic islet cell autoantibodies must be assessed in the past 6 months and on at least two separate occasions. A greater than or equal to 10% increase in HbA1c compared to baseline qualifies as dysglycemia. New Standards of Care in Diabetes - 2025 published.