# PRIOR AUTHORIZATION POLICY

**POLICY:** Diabetes – Tzield Prior Authorization Policy
- Tzield™ (teplizumab-mzwv intravenous infusion – Provention/Sanofi)

**REVIEW DATE:** 11/30/2022

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## OVERVIEW

Tzield, an anti-CD3 monoclonal antibody, is indicated to **delay the onset of Stage 3 type 1 diabetes** in adults and pediatric patients ≥ 8 years of age with Stage 2 type 1 diabetes.

Tzield is administered by intravenous infusion (over a minimum of 30 minutes) using body surface area-based dosing, once daily for 14 consecutive days.[1] Prior to initiating Tzield, obtain a complete blood count and liver enzyme tests. Use of Tzield is not recommended in patients with certain laboratory abnormalities, including lymphopenia, anemia, thrombocytopenia, neutropenia, or increased liver enzymes. Refer to the prescribing information for specific thresholds. Additionally, patients with laboratory or clinical evidence of acute infection with Epstein-Barr virus or cytomegalovirus should not receive Tzield, nor should patients with active serious infection or chronic active infection other than localized skin infections.

## Clinical Efficacy

Efficacy of Tzield among patients at risk for development of type 1 diabetes was evaluated in one pivotal study called TN-10 (published) [n = 76].[2] Eligible patients were non-diabetic relatives of patients with type 1 diabetes and were ≥ 8 years of age at the time of randomization. Patients were also required to have two or more diabetes-related autoantibodies, confirmed on at least two occasions, within 6 months before randomization. In addition, patients were required to have had evidence of dysglycemia during an oral glucose tolerance test (OGTT). An abnormal OGTT was defined as meeting one of the following: fasting plasma glucose ≥ 110 to < 126 mg/dL; 2-hour postprandial plasma glucose ≥ 140 to < 200 mg/dL; or 30-, 60-, or 90-minute postprandial plasma glucose ≥ 200 mg/dL. Initially, two OGTTs were required within 52 days of enrollment; however, a protocol amendment was put in place requiring only one abnormal glucose tolerance test result for patients < 18 years of age.

## Guidelines

American Diabetes Association (ADA) Standards of Care (2022) comment on available data with Tzield but do not make recommendations regarding its use.[3] According to the ADA Standards, screening for pre-symptomatic type 1 diabetes using screening tests that detect autoantibodies to insulin, glutamic acid decarboxylase (GAD), islet antigen 2, or zinc transporter 8 is currently recommended in the setting of a research study or can be considered as an option for first-degree family members of a proband with type 1 diabetes (Level B recommendation).[3] Development of and persistence of multiple islet autoantibodies is a risk factor for clinical diabetes and may serve as an indication for intervention in the setting of a clinical trial or screening for Stage 2 type 1 diabetes (Level B recommendation).

According to the ADA Standards, three distinct stages of type 1 diabetes can be identified, which serve as a framework for future research and regulatory decision-making.[3] Clinical type 1 diabetes is referred to as "Stage 3 type 1 diabetes" and is characterized by new-onset hyperglycemia and presence of symptoms. Diagnostic criteria include involve one of the following: fasting plasma glucose (FPG) ≥ 126 mg/dL; 2-hour postprandial glucose ≥ 200 mg/dL during an OGTT (75 grams); glycosylated hemoglobin ($HbA_{1C}$) ≥ 6.5%; or random plasma glucose ≥ 200 mg/dL for a patient with classic symptoms of hyperglycemia or hyperglycemic crisis. "Stage 1 type 1 diabetes" and "Stage 2 type 1 diabetes" are pre-symptomatic states characterized by autoimmunity (i.e., multiple autoantibodies) but no overt diabetes symptoms. In Stage 1

disease, glycemia is normal. In Stage 2 disease, dysglycemia is present but below the threshold considered overt or Stage 3 type 1 diabetes. Dysglycemia in Stage 2 type 1 diabetes involves FPG 100 to 125 mg/dL; 2-hour postprandial glucose 140 to 199 mg/dL; $HbA_{1C}$ 5.7% to 6.4%; or a ≥ 10% increase in $HbA_{1C}$.

## POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Tzield. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Tzield as well as the monitoring required for adverse events and long-term efficacy, approval requires Tzield to be prescribed by or in consultation with a physician who specializes in the condition being treated. For certain criteria, verification is required as noted by **[verification required by prescriber]**. All reviews (approvals and denials) will be forwarded to the Medical Director for evaluation.

**Documentation:** Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to chart notes, laboratory tests, claims records, and/or other information.

**Automation:** None.

## RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tzield is recommended in those who meet the following criteria:

### FDA-Approved Indication

1. **Type 1 Diabetes (Clinical/Stage 3), Delay of Onset.** Approve for a one-time per lifetime course (14-day course) if the patient meets the following criteria (A, B, C, D, E, F, G, H, I, J, and K):
   - **A)** Patient is ≥ 8 years of age; AND
   - **B)** Patient does NOT have a clinical diagnosis of type 1 diabetes (i.e., Stage 3 type 1 diabetes); AND
     Note: Clinical type 1 diabetes is also referred to as Stage 3 type 1 diabetes. "Stage 1 type 1 diabetes" and "Stage 2 type 1 diabetes" are considered preclinical states and would not fall into the category of clinical type 1 diabetes.
   - **C)** Patient does NOT have type 2 diabetes; AND
   - **D)** Patient has at least one biological relative with a diagnosis of type 1 diabetes; AND
     Note: Examples of relatives include first-degree relatives (e.g., parent, sibling) or other relatives (e.g., grandparent, aunt, uncle, cousin).
   - **E)** Patient has tested positive for at least TWO of the following type 1 diabetes-related autoantibodies on two separate occasions: anti-glutamic acid decarboxylase 65 (anti-GAD65); anti-islet antigen-2 (anti-IA-2); islet-cell autoantibody (ICA); micro insulin; anti-zinc transporter 8 (anti-ZnT8) **[documentation required]**.
     Note: The patient needs to have tested positive on two separate occasions, with at least two positive autoantibodies per occasion; however, the patient does not have to be positive for the same two antibodies on both occasions. For example, a positive test for anti-GAD65 and anti-IA-2 on one occasion, and positive test for ICA and micro insulin on another occasion would satisfy the requirement.
   - **F)** Patient meets both of the following (i and ii) **[documentation required]**:
     - **i.** Patient has taken an oral glucose tolerance test within the preceding 2 months; AND
     - **ii.** The results of the oral glucose tolerance test indicated dysglycemia by meeting at least one of the following (a, b, or c):
       - **a)** Fasting plasma glucose level ≥ 110 to < 126 mg/dL; OR

**b)** 2-hour postprandial plasma glucose level ≥ 140 to < 200 mg/dL; OR
**c)** Intervening postprandial glucose level at 30, 60, or 90 minutes > 200 mg/dL; AND

**G)** At baseline (prior to the initiation of Tzield), patient does NOT have evidence of hematologic compromise, as defined by meeting the following (i, ii, iii, and iv) **[documentation required]**:
- **i.** Lymphocyte count ≥ 1,000 lymphocytes/mcL; AND
- **ii.** Hemoglobin ≥ 10 g/dL; AND
- **iii.** Platelet count ≥ 150,000 platelets/mcL; AND
- **iv.** Absolute neutrophil count ≥ 1,500 neutrophils/mcL; AND

**H)** At baseline (prior to the initiation of Tzield), patient does NOT have evidence of hepatic compromise, as defined by meeting the following (i, ii, and iii) **[documentation required]**:
- **i.** Alanine aminotransferase (ALT) ≤ 2 times the upper limit of normal (ULN); AND
- **ii.** Aspartate aminotransferase (AST) ≤ 2 times the ULN; AND
- **iii.** Bilirubin ≤ 1.5 times the ULN; AND

**I)** According to the prescriber, the patient does NOT have any of the following (i, ii, or iii):
- **i.** Laboratory or clinical evidence of acute infection with Epstein-Barr Virus or cytomegalovirus; OR
- **ii.** Active serious infection; OR
- **iii.** Chronic active infection (other than localized skin infection); AND

**J)** Patient has NOT received Tzield in the past **[verification required by prescriber]**; AND
Note: Verify through claims that the patient has not previously received Tzield AND, if no claim for Tzield is present, the prescriber must attest that the patient has not previously received Tzield.

**K)** The medication will be prescribed by an endocrinologist.

## CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tzield is not recommended in the following situations:

1. **Type 1 Diabetes (Clinical/Stage 3), Treatment.** Note: Clinical type 1 diabetes is also referred to as Stage 3 type 1 diabetes. "Stage 1 type 1 diabetes" and "Stage 2 type 1 diabetes" are considered preclinical states and would not fall into the category of clinical type 1 diabetes.
   Tzield is not indicated for patients with a diagnosis of clinical type 1 diabetes (i.e., Stage 3 type 1 diabetes).

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

## REFERENCES

1. Tzield™ intravenous infusion [prescribing information]. Red Bank, NJ: Provention; November 2022.
2. Herold KC, Bundy BN, Long SA, et al; Type 1 Diabetes TrialNet Study Group. An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes. *N Engl J Med*. 2019 Aug 15;381(7):603-613.
3. American Diabetes Association. Standards of medical care in diabetes – 2022. *Diabetes Care*. 2022;45(Suppl 1):S1-S258.