POLICY: Diabetes – Tzield

- Tzield™ (teplizumab-mzwv intravenous infusion – Provention/Sanofi)

EFFECTIVE DATE: 3/15/2023
LAST REVISION DATE: 11/13/2024

COVERAGE CRITERIA FOR: All Aspirus Medicare Plans

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 (2024) state that Tzield should be considered in selected individuals ≥ 8 years with stage 2 type 1 diabetes to delay the onset of symptomatic type 1 diabetes (Level B recommendation).[3] Management should be in a specialized setting with appropriately trained personnel. According to the ADA Standards, screening for pre-symptomatic type 1 diabetes may be done by detection of autoantibodies to insulin, glutamic acid decarboxylase (GAD, GAD65), islet antigen 2 (IA-2 and IA-2b), or zinc transporter 8 (Level B recommendation).[3] The presence of multiple islet autoantibodies is a risk factor for clinical diabetes. Testing for dysglycemia may be used to further forecast near-term risk. When multiple islet autoantibodies are identified, referral to a specialized center for further evaluation and/or consideration of a clinical trial or approved therapy to potentially delay the development clinical diabetes should be considered (Level B recommendation). A consensus guidance for monitoring individuals with islet autoantibody-positive pre-stage 3 type 1 diabetes (2024) state that when patients who are insulin autoantibody positive are initially identified, there is a need for confirmation using a second

sample.[4] Similar to the ADA Standards of Care, the guidance recommends that interested patients with stage 2 type 1 diabetes be offered trial participation or approved therapies.

Table 1. Autoantibodies Against Islet Autoantigens Detected in Stage 1 to 3 Type 1 Diabetes.[4]

Autoantibody	Islet Specificity	Typical Characteristics
IAA	Insulin	• Common as a first autoantibody in young children • More common in younger children • Frequency decreases with age • Not informative for individuals treated with insulin
GADA	GAD	• Common as a first autoantibody in childhood to age 15 years • Adult-onset cases most often present with GADA • Associated with slower progression to type 1 diabetes and often found as a single positive islet autoantibody, especially in adults.
IA-2A (also called ICA512)	Tryosine phosphate islet antigen-2	Associated with more advanced islet autoimmunity and faster progression to stage 3 type 1 diabetes
ZnT8A	Zine transporter type 8, a transmembrane protein in the β-cell granule	Presence can improve risk stratification in individuals with single GADA+, IAA+, or IA-2A+ status
ICA	Multiple antigens, undefined	Detected by indirect immunofluorescence on islet cell tissue. While not frequently measured other than in research studies, it does add to risk determination in the presence of other biochemical autoantibodies

IAA – Insulin autoantibody; GADA - Glutamic acid decarboxylase autoantibody; IA-2A – Insulinoma antigen-2 autoantibody; ICA512 – Islet cell autoantigen 512; ICA – Islet cell autoantibodies.

According to the ADA Standards, three distinct stages of type 1 diabetes can be identified.[3] Clinical type 1 diabetes is referred to as "Stage 3 type 1 diabetes" and is characterized by overt hyperglycemia and the presence of symptoms. Diagnostic criteria include one of the following: fasting plasma glucose (FPG) ≥ 126 mg/dL; 2-hour postprandial glucose ≥ 200 mg/dL during an OGTT (75 grams); hemoglobin A_{1c} (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, patients have a normal glycemic level. In Stage 2 disease, dysglycemia is present but below the threshold considered overt for 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}.

Screening for Type 1 Diabetes Risk

Multiple studies indicate that measuring islet autoantibodies in relatives of those with type 1 diabetes or in children from the general population can effectively identify those who will develop type 1 diabetes.[3] A study reported the risk of progression to type 1 diabetes from the time of seroconversion to autoantibody positivity in pediatric cohorts from three countries. Of the 585 children who developed more than two autoantibodies, nearly 70% developed type 1 diabetes within 10 years and 84% developed type 1 diabetes within 15 years. These findings are highly significant because while the one group of patients was recruited from children of parents with type 1 diabetes, the other two groups were recruited from the general population. The findings in all three groups were the same, suggesting that the same sequence of events led to clinical disease in both "sporadic" and familial cases of type 1 diabetes. The risk of type 1 diabetes increases as the number of relevant autoantibodies detected increases.

Family history of autoimmune diabetes and personal or family history of allergic diseases or other autoimmune diseases increases risk of autoimmune diabetes compared with the general population.[3] Individuals who test autoantibody positive should be either provided with or referred for counseling about the risk of developing diabetes, diabetes symptoms, diabetic ketoacidosis prevention, and consideration of

additional testing as applicable to help determine if they meet criteria for intervention aimed at delaying progression.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Tzield. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

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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 ALL of the following (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

2. 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.

A) Patient does NOT have type 2 diabetes; AND

B) Patient has at least one biological relative with a diagnosis of type 1 diabetes; AND

3. Note: Examples of relatives include first-degree relatives (e.g., parent, sibling) or other relatives (e.g., grandparent, aunt, uncle, cousin).

A) 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]**.

4. 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.

5. F) Patient meets ONE of the following (i, ii, or iii) **[documentation required]**:

i. Patient has a 2-hour postprandial glucose level ≥ 140 to < 200 mg/dL during an oral glucose tolerance test in the preceding 2 months; OR

ii. Patient has a fasting plasma glucose level ≥ 100 to < 126 mg/dL in the preceding 2 months; OR

iii. Patient has an $HbA_{1c} \geq 5.7\%$ to $< 6.5\%$ in the preceding 2 months. 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 history 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.

6.

Dosing. Approve a one-time, 14-day course of Tzield with the following regimen (A, B, C, D, and E):

A) 65 mcg/m^2 body surface area (BSA) given intravenously on Day 1; AND

B) 125 mcg/m^2 BSA given intravenously on Day 2; AND

C) 250 mcg/m^2 BSA given intravenously on Day 3; AND

D) 500 mcg/m^2 BSA given intravenously on Day 4; AND

E) 1,030 mcg/m^2 BSA given intravenously once daily on Days 5 through 14.

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.

   7. Tzield is not indicated for patients with a diagnosis of clinical type 1 diabetes (i.e., Stage 3 type 1 diabetes).

   8.
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; December 2023.
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 – 2024. *Diabetes Care*. 2024;47(Suppl 1):S1-S321.
4. Phillip M, Achenbach P, Adala A, et al. Consensus guidance for monitoring individuals with islet autoantibody-positive pre-stage 3 type 1 diabetes. *Diabetes Care*. 2025;47:1276-1298.

5. American Diabetes Association. Standards of medical care in diabetes – 2023. *Diabetes Care*. 2023;46(Suppl 1):S1-S291.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	11/30/2022
Annual Revision	**Type 1 Diabetes (Clinical/Stage 3), Delay of Onset.** Glycemic criteria for the diagnosis of Stage 2, Type 1 diabetes was revised. The criterion related to fasting plasma glucose was modified to remove the requirement that the result of the test comes from an oral glucose tolerance test. Additionally, the definition of the fasting plasma glucose value was modified to ≥ 100 mg/dL to < 126 mg/dL (previously, fasting plasma glucose was defined as a value of ≥ 110 mg/dL to < 126 mg/dL). The criterion for an intervening postprandial glucose level at 30, 60, or 90 minutes of > 200 mg/dL based on an oral glucose tolerance test within the preceding 2 months was removed. A new criterion was added, such that an HbA_{1c} of ≥ 5.7% to < 6.5% in the preceding 2 months is an option for diagnosis. The updated set of glycemic criteria for the diagnosis of Stage 2, Type 1 diabetes now reads that the patient meets ONE of the following [documentation required]: Patient has a 2-hour postprandial glucose level ≥ 140 mg/dL to < 200 mg/dL during an oral glucose tolerance test in the preceding 2 months (no change to this criterion); OR, Patient has a fasting plasma glucose level of ≥ 100 mg/dL to < 126 mg/dL in the preceding 2 months (see change described above); OR, Patient has an HbA_{1c} of ≥ 5.7% to < 6.5% in the preceding 2 months (new criterion, see above).	11/15/2023
Aspirus P&T Review	Policy reviewed and approved by Aspirus P&T committee. Annual review process	09/16/2024
Annual Revision	No criteria changes.	11/13/2024