Drug Coverage Policy

Effective Date.....5/1/2026
Coverage Policy Number.....IP0537
Policy Title.....Tzield

Diabetes – Tzield

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

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

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.[1]

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 (i.e., autoantibodies to microinsulin [mIAA], glutamic acid decarboxylase 65 [GAD65], and insulinoma-associated antigen-2 [IA-2, or ICA512], islet cell autoantibody (ICA) and zinc transporter 8 [ZnT8]), confirmed on at least two occasions, within 6 months before randomization. In addition, patients were required to have 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 (2025) 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 (stage 3) 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 (IAA), glutamic acid decarboxylase (GAD, GAD65), islet antigen-2 (IA-2 and IA-2b), or ZnT8 (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). Other scientific statements and/or guidelines provide similar recommendations for screening pre-symptomatic type 1 diabetes by detection of autoantibodies (i.e., GAD autoantibodies, IAA, insulinoma antigen-2 autoantibodies [IA-2A], or ZnT8 autoantibodies).[5,6]

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 is 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.

Coverage Policy

POLICY STATEMENT

Prior Authorization is required for 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. All documentation must include patient-specific identifying information.

Tzield is considered medically necessary when the following criteria are met:

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 ALL of the following (A, B, C, D, E, F, G, H, I, and J):
   - **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 tested positive for at least TWO of the following type 1 diabetes-related autoantibodies on two separate occasions: glutamic acid decarboxylase 65 (GAD65) autoantibody; islet antigen-2 (IA-2) autoantibody [also referred to as insulinoma-associated antigen-2 autoantibody {IA-2A}]; islet-cell autoantibody (ICA); insulin

autoantibody (IAA); zinc transporter 8 (ZnT8) autoantibody **[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 GAD65 and IA-2 on one occasion, and positive test for ICA and IAA on another occasion would satisfy the requirement.

E) 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} ≥ 5.7% to <6.5% in the preceding 2 months; AND

F) At baseline (prior to the initiation of Tzield), patient does NOT have evidence of hematologic compromise, as defined by meeting ALL of 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

G) At baseline (prior to the initiation of Tzield), patient does NOT have evidence of hepatic compromise, as defined by meeting ALL of 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

H) 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

I) 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.

J) The medication will be prescribed by an endocrinologist.

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 Covered

Tzield for any other use is considered not medically necessary, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Type 1 Diabetes (Clinical/Stage 3), Treatment.** 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). The PROTECT trial randomized patients ≥ 8 to < 18 years of age with stage 3 type 1 diabetes to Tzield or placebo for two 12-day courses of therapy (n = 328). Patients had been diagnosed with type 1 diabetes within 6 weeks of randomization. In addition, patients had at least one autoantibody associated with type 1 diabetes (antibodies against glutamic acid decarboxylase, zinc transporter 8, insulin, islet cell, or islet antigen-2) and a peak stimulated C-peptide level of ≥ 0.2 pmol/mL. The primary endpoint was the change from baseline in C-peptide levels at Week 78. Key secondary endpoints were: the mean of patients' daily insulin dose (units/kg/day), the mean daily percentage of time in the target glucose range, the change from baseline in the mean hemoglobin A_{1c}, and clinically important hypoglycemic events (defined as a blood glucose level < 54 mg/dL, severe cognitive impairment requiring assistance for recovery, or both) at Week 78. The mean change from baseline in C-peptide area under the concentration time curve levels at Week 78 was significantly larger with Tzield vs. placebo. No significant differences were shown for the secondary endpoints, intended to determine the effect of Tzield on clinical variables. The BETA PRESERVE trial has been initiated to assess the change in glycemic control and prandial insulin dependency with Tzield vs. placebo in patients with recently diagnosed stage 3 type 1 diabetes.[8]

Coding Information

1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J9381	Injection, teplizumab-mzwv, 5 mcg

References

1. Tzield® intravenous infusion [prescribing information]. Morristown, NJ: Provention/Sanofi; April 2025.
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 – 2025. *Diabetes Care*. 2025;48(Suppl 1):S1-S352.

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. Mehta S, Ryabeta-Linehard A, Patel N, et al. Pediatric Endocrine Society statement on consideration for use of teplizumab (Tzield™) in clinical practice. *Horm Res Paediatr.* 2025;98:597-608.
6. Michels AW, Brusko TM, Evans-Molina CE, et al. Challenges and opportunities for understanding the pathogenesis of type 1 diabetes: An Endocrine Society Scientific Statement. *J Clin Endorinol Metab.* 2025;110:2496-2508.
7. Ramos EL, Dyan CM, Chatenoud L, et al; for the PROTECT Study Investigators. Teplizumab and β-cell function in newly diagnosed type 1 diabetes. *N Engl J Med.* 2023;389:2151-2161.
8. Sanofi. A study to investigate efficacy and safety of teplizumab compared with placebo in participants 1 to 25 years of age with stage 3 type 1 diabetes (BETA PRESERVE). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2025 11 Nov]. Available at: https://clinicaltrials.gov/study/NCT07088068. NLM Identifier: NCT07088068.

Revision Details

Summary of Changes	Review Date	Effective Date
Policy Title: **Updated** coverage policy title. **Type 1 Diabetes (Clinical/Stage 3), Delay of Onset:** **Updated** criterion definition of fasting plasma glucose value. **Added** criterion screening A1C. **Removed** criterion one biological relative with type 1 diabetes diagnosis. **Removed** coding information from policy.	1/02/2024	04/01/2024
Updated coding: **Added** J9381	-	9/10/2024
No criteria changes.	12/05/2024	1/15/2025
Type 1 Diabetes (Clinical/Stage 3), Delay of Onset: **Removed** "intervening postprandial glucose level at 30, 60, or 90 minutes greater than 200 mg/dL." **Removed** "results of acute first phase insulin response (FPIR) during an intravenous glucose tolerance test (IVGTT) demonstrate rise in serum insulin below the first percentile of normal during the first 10 minutes after IV glucose challenge." **Removed** criteria "i. Adequate hematologic function ii. Adequate hepatic function" from "Prescriber attests to ALL of the following:" **Added** "Patient has at least one biological relative with a diagnosis of type 1 diabetes." **Added** "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."	12/18/2025	2/1/2026

Added "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." **Added** "Chronic active infection (other than localized skin infection)" **to** "According to the prescriber, the patient does NOT have any of the following:" **Added** "**[verification required by prescriber]**" **to** "Patient has NOT received Tzield in the past.		
Type 1 Diabetes (Clinical/Stage 3), Delay of Onset: Removed "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)."	4/16/2026	5/1/2026

The policy effective date is in force until updated or retired.

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