Drug Coverage Policy

Effective Date.....9/1/2026
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:[1]

- **Delay the onset of Stage 3 type 1 diabetes** in adults and pediatric patients ≥ 1 year of age with **Stage 2 type 1 diabetes**.
- **Delay the decline in endogenous insulin production** in pediatric patients 8 to 17 years of age **recently diagnosed with Stage 3 type 1 diabetes**.

The indication to delay the decline in endogenous insulin production in pediatric patients with recently diagnosed Stage 3 type 1 diabetes is approved under accelerated approval based on evidence of reduced C-peptide decline.[1] Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

Limitations of Use: There is limited evidence of safety and effectiveness in patients ≥ 45 years of age with Stage 2 type 1 diabetes.[1] Tzield is not effective as a disease modifying therapy in non-autoimmune dysglycemic conditions.

Patient Selection
Stage 2 Type 1 Diabetes
A patient with Stage 2 type 1 diabetes should be selected for treatment with Tzield to delay the onset of Stage 3 type 1 diabetes based on the confirmation of at least two positive pancreatic islet cell autoantibodies AND dysglycemia without over hyperglycemia using an oral glucose tolerance test (OGTT) [if not available, an alternative method for diagnosing dysglycemia without overt hyperglycemia may be appropriate].[1]

Ensure the patient's diagnosis confirms an autoimmune origin and does not suggest type 2 diabetes or other forms of diabetes.[1] These may include, but are not limited to genetic forms of diabetes, maturity-onset diabetes of the young, latent autoimmune diabetes in adults, or diabetes secondary to medication or surgery.

Stage 3 Type 1 Diabetes
A patient with Stage 3 type 1 diabetes should be selected for treatment with Tzeild to delay the decline in endogenous insulin production in recently diagnosed (within the last 8 weeks) Stage 3 type 1 diabetes based on the confirmation of at least one positive pancreatic islet cell autoantibody AND peak C-peptide on a mixed-meal tolerance test (if a mixed meal tolerance test is not available, an alternative method for measuring peak C-peptide may be appropriate).

Laboratory Evaluation
Prior to initiating Tzield, obtain a complete blood count and liver enzyme tests.[1] Tzlied is not recommended in patients with the following: Lymphocyte count < 1,000 lymphocytes/mcL; hemoglobin < 10 g/dL; platelet count < 150,000 platelets/mcL; elevated alanine aminotransferase or aspartate aminotransferase > 2-times the upper limit of normal (ULN) or bilirubin > 1.5-times the ULN; or active serious infection or chronic active infection other than localized skin infections. Additionally, patients should be evaluated for active Epstein-Barr virus or cytomegalovirus. Use of Tzield is Contraindicated in patients who are immunocompromised or have active viral infection.

Dosing
Stage 2 Type 1 Diabetes
Tzield is administered by intravenous infusion using body surface area-based dosing, once daily for 14 consecutive days as outlined in Table 1.[1] The infusion is given over 30 minutes in adult and pediatric patients ≥ 8 years of age and over 2 hours in pediatric patients ≥ 1 year to < 8 years of age.

Table 1. Stage 2 Type 1 Diabetes: Recommended Dosing for Tzield.[1]

Treatment Day	Tzield Dose
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

Stage 3 Type 1 Diabetes
Initiate treatment as soon as possible following Stage 3 type 1 diagnosis but no later than 8 weeks from diagnosis.[1] Administer Tzield by intravenous infusion over a minimum of 30 minutes, once daily for 12 consecutive days for each treatment course, for a total of two treatment courses. Administer the second 12-day treatment course 6 months after the first treatment course.[1] If the second course is delayed, administer the second treatment course within 6 to 12 months after the first treatment course.

Table 2. Stage 3 Type 1 Diabetes: Recommended Dosing for Tzield.[1]

Treatment Day	Tzield Dose
Day 1	106 mcg/m^2
Day 2	425 mcg/m^2
Day 3 through 12	850 mcg/m^2

Note: Tzield is administered once daily for 12 consecutive days for each treatment course, for a total of two treatment courses.

Clinical Efficacy
Stage 2 Type 1 Diabetes
The 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., microinsulin autoantibody [mIAA], glutamic acid decarboxylase 65 [GAD65] autoantibody, and insulinoma-associated antigen-2 [IA-2 or ICA512] autoantibody, islet cell autoantibody (ICA) or zinc transporter 8 [ZnT8] autoantibody), confirmed on at least two occasions, within 6 months before randomization. In addition, patients were required to have had evidence of dysglycemia during an OGTT. An abnormal OGTT was defined as meeting one of the following: fasting plasma glucose (FPG) ≥ 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.

The PETITE-T1D trial is an ongoing, 2-year, single-arm, open-label, multicenter study evaluating the safety and pharmacokinetics of Tzield in children < 8 years of age with Stage 2 type 1 diabetes (n = 23).[9] Eligible patients were required to have two or more islet autoantibodies, including GAD autoantibody, IA-2 autoantibody, insulin autoantibody (IAA), ZnT8 autoantibody, or ICA, and evidence of dysglycemia without overt hyperglycemia. Dysglycemia was defined as FPG ≥ 100 mg/dL to ≤ 125 mg/dL, a 2-hour plasma glucose of ≥ 140 mg/dL to ≤ 199 mg/dL, a hemoglobin A_{1c} (HbA_{1c}) of ≥ 5.7% to ≤ 6.4%, or a ≥ 10% increase in HbA_{1c}. Among enrolled patients, 34.8% had three positive autoantibodies and 34.8% had four positive autoantibodies; 13% of patients had two positive autoantibodies and 17.4% of patients had five positive autoantibodies. A family history of type 1 diabetes was present in 87% of patients but was not required for study eligibility. A prespecified interim analysis was conducted after 15 patients completed 1 year of post-treatment follow-up. At the time of the analysis, all 23 patients had received Tzield, with 10 patients completing the full 14-day treatment course. Two patients met criteria for progression to Stage 3

type 1 diabetes. The estimated probability of remaining free from progression to Stage 3 type 1 diabetes was 89.6% (95% confidence interval: 64.3% to 97.3%) at the time of the interim analysis.

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).[7] The two courses of Tzield were to be administered 26 days apart; however, due to the Coronavirus-19 pandemic restriction, the protocol was amended, on the basis of safety and efficacy data from earlier studies, to allow patients to delay the second 12-day course to approximately Week 52, if needed. Patients had been diagnosed with Stage 3 type 1 diabetes within 6 weeks of randomization. In addition, patients had at least one autoantibody associated with type 1 diabetes (antibodies against GAD65, ZnT8, insulin autoantibody [IAA], ICA, or IA-2) AND a peak stimulated C-peptide level of ≥ 0.2 pmol/mL from a 2-hour mixed meal tolerance test. The primary endpoint was the change from baseline in C-peptide levels at Week 78. C-peptide levels were determined from the area under the concentration-time curve (AUC) during a 4-hour mixed-meal tolerance test. Key secondary endpoints were: the mean of the 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 HbA_{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. Tzield-treated patients had significantly higher stimulated C-peptide levels at Week 78 (least-squares mean difference 0.13 pmol/mL; 95% confidence interval 0.09, 0.17; P < 0.001), representing a 59.3% difference favoring Tzield. At Week 78, 94.9% vs. 79.2% of Tzield- and placebo-treated patients, respectively, maintained a clinically meaningful peak C-peptide ≥ 0.2 pmol/mL. No significant differences were shown for the secondary endpoints, intended to determine the effect of Tzield on clinical variables. HbA_{1c} was rapidly controlled in both groups, and differences in time in target glucose range and insulin dose did not reach statistical significance

An unpublished extension of the TN-10 trial followed patients previously randomized to a 14-day course of Tzield or placebo (for Stage 2 type 1 diabetes) and then received a 12-day course of Tzield after developing Stage 3 type 1 diabetes.[10] Patients within 1 year of Stage 3 type 1 diabetes diagnosis received a 12-day course of Tzield with up to 78 weeks of follow-up. The mean time from Stage 3 type 1 diabetes diagnosis to the Tzield dose was 36.8 weeks. The mean HbA_{1c} was 7.22%, the mean average daily insulin dose was 0.34 units/kg/day, and the mean C-peptide was 0.685 ln(AUC+1). Six patients (age range 12 years to 44 years) received Tzield; five of these patients previously received Tzield in TN-10 and one patient previously received placebo. Five patients received all 12 doses of Tzield for Stage 3 type 1 diabetes; one patient received 11 doses. At Week 78, the mean HbA_{1c} was 8.5%, the mean daily insulin dose was 0.54 units/kg/day, and the mean C-peptide was 0.549 ln(AUC+1). One patient met criteria for insulin discontinuation. All patients had at least one treatment-emergent adverse event. One patient had treatment-related cytokine release syndrome (Garde 1, fully resolved).

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]

Guidelines
The indication for Tzield in early Stage 3 type 1 diabetes is not addressed as an approved therapy in available guidelines. American Diabetes Association (ADA) Standards of Care (2026) state there are currently no approved therapies for the preservation of C-peptide or prolongation of the partial remission (honeymoon) phase in individuals with established Stage 3 type 1 diabetes.[3] It is noted that higher C-peptide levels have been associated with better HbA_{1c}, lower risk of retinopathy, lower risk of nephropathy, and lower risk of severe hypoglycemia. Various therapies, including Tzield are under active investigation.

ADA Standards of Care (2026) 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) [the Standards were published prior to approval of a lower age indication for Tzield].[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 IAA, glutamic acid decarboxylase (GAD, GAD65), IA-2 and IA-2b, or ZnT8 (Level B recommendation).[3] Autoantibody-based screening for presymptomatic type 1 diabetes should be offered to those with a family history of type 1 diabetes or otherwise known elevated genetic risk (Level B recommendation). In individuals with screening results positive for one or more islet autoantibody, further evaluation for Stage 3 type 1 diabetes is recommended (Level B recommendation). Individuals with multiple confirmed islet autoantibodies and without over type 1 diabetes have a high risk for progression to Stage 3 type 1 diabetes and should be referred 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). Individuals with a single confirmed IA-2 autoantibody should be monitored similarly to individuals with multiple islet autoantibodies because IA-2 autoantibody positivity is an independent risk factor for progression (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, IA-2 autoantibodies, 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 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. In several cohort studies, up to 50% of children with only a single autoantibody revert to being islet autoantibody negative during follow-up. Therefore, it is recommended that the first autoantibody-positive test be confirmed with a second test within 3 months,

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 ONE of the following criteria are met:

FDA-Approved Indication

1. **Stage 2 Type 1 Diabetes.** Approve for 30 days if the patient meets ALL of the following (A, B, C, D, E, F, G, H, and I):
   Note: This is to delay the onset of Stage 3 type 1 diabetes in a patient with Stage 2 type 1 diabetes.
   - **A)** Patient is ≥1 year 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 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.

D) 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

E) 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

F) 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 ≤ 2 times the upper limit of normal ; AND
- ii. Aspartate aminotransferase ≤ 2 times the upper limit of normal; AND
- iii. Bilirubin ≤ 1.5 times the upper limit of normal; AND

G) 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

H) 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.

I) The medication will be prescribed by an endocrinologist.

Dosing. Approve a one-time, 14-day course of Tzield per lifetime with the following dosing (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.

2. Stage 3 Type 1 Diabetes. Approve for 1 year if patient meets ALL of the following (A, B, C, D, E, F, G, H, and I):

Note: This is to delay the decline in endogenous insulin production in a patient with recently diagnosed Stage 3 type 1 diabetes.

A) Patient is ≥ 8 years of age and ≤ 17 years of age; AND

B) Patient meets BOTH of the following (i and ii):

i. Patient has been diagnosed with Stage 3 type 1 diabetes confirmed by ONE of the following (a, b or c) **[documentation required]**:

a) Patient had, or patient currently has a 2-hour plasma glucose ≥ 200 mg/dL; OR

b) Patient had, or patient currently has a fasting plasma glucose ≥ 126 mg/dL; OR

c) Patient had, or patient currently has an HbA_{1c} ≥ 6.5%; AND

ii. Diagnosis is ≤ 8 weeks prior to the first dose of Tzield.

C) Patient has tested positive for at least ONE of the following type 1 diabetes-related autoantibodies: 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]**; AND

D) Patient has a peak C-peptide level ≥ 0.2 pmol/mL on a mixed-meal tolerance test or an alternative method **[documentation required]**; AND

E) 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

F) 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 ≤ 2 times the upper limit of normal; AND

ii. Aspartate aminotransferase ≤ 2 times the upper limit of normal; AND

iii. Bilirubin ≤ 1.5 times the upper limit of normal; AND

G) 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

H) Patient meets ONE of the following (i or ii):

Note: A patient should not receive more than two courses of Tzield in their lifetime. One course of Tzield consists of one 14-day course (recommended dose in a patient with Stage 2 type 1 diabetes) OR one 12-day course (recommended dose in a patient with Stage 3 type 1 diabetes). Two lifetime courses of Tzield consist of either one 14-day course of Tzield + one 12-day course of Tzield or two 12-day courses of Tzield.

i. Patient has NOT received Tzield in the past **[verification required by prescriber]**; OR

Note: Verify through claims history that the patient has not previously received Tzield. If no claim for Tzield is present, the prescriber must attest that the patient has not previously received Tzield.

ii. Patient has NOT received more than one course of Tzield in the past; **[verification required by prescriber]**; AND

Note: Verify through claims history that the patient has not previously received more than one course of Tzield. If no claim for Tzield is present, the prescriber must attest that the patient has not previously received Tzield. If a claim is present, the prescriber must attest that the patient has NOT received more than one course of Tzield.

I) The medication will be prescribed by an endocrinologist.

Dosing. Approve up to two, 12-day treatment courses of Tzield per lifetime with the following dosing (A, B, and C):
A) 106 mcg/m^2 body surface area (BSA) given intravenously on Day 1; AND
B) 425 mcg/m^2 BSA given intravenously on Day 2; AND
C) 850 mcg/m^2 BSA given intravenously on Days 3 through 12.

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 2 Diabetes.** Tzield is not indicated for type 2 diabetes.[1]

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; June 2026.
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.
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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 15 June 2026]. Available at: Study Details | NCT07088068 | 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 | ClinicalTrials.gov. NLM Identifier: NCT07088068.
9. Gitelman SE, Simmons K, Sherr JL, et al. Safety and pharmacokinetics of teplizumab in children less than 8 years of age with stage 2 type 1 diabetes. *Diabetologia*. 2025;69:330-342.
10. Herold KC, Sherr JL, Haller MJ, et al. TN-10 extension study – teplizumab following Stage 3 type 1 diabetes diagnosis in participants from the TN-10 trial [abstract 840-P]. Presented at: the American Diabetes Association (ADA) 85th Scientific Sessions; San Diego, CA; June 20-24, 2025.

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." **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	12/18/2025	2/1/2026

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
Type 1 Diabetes (Clinical/Stage 3), Delay of Onset. **Updated from** "Patient is ≥8 years of age" **to** "Patient is ≥1 year of age" **Removed "**Patient does NOT have type 2 diabetes" (moved to Conditions Not Covered) **Conditions Not Covered** **Added** Type 2 Diabetes as a Condition Not Covered	5/14/2026	6/15/2026
Updated from "Type 1 Diabetes (Clinical/Stage 3), Delay of Onset" **to** "Stage 2 Type 1 Diabetes" **Added** new condition of approval "**Stage 3 Type 1 Diabetes**" **Removed** from Conditions Not Covered "Type 1 Diabetes (Clinical/Stage 3), Treatment"	7/16/2026	9/1/2026

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

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