

Clinical Policy: Teplizumab-mzwv (Tziel)

Reference Number: PA.CP.PHAR.492

Effective Date: 01/2023

Last Review Date: 05/2026

Description

Teplizumab-mzwv (Tziel®) is a CD3-directed antibody.

FDA Approved Indication(s)

Tziel is indicated to:

- Delay the onset of Stage 3 type 1 diabetes (T1D) in adults and pediatric patients 1 year of age and older with Stage 2 T1D.
- Delay the decline in endogenous insulin production in pediatric patients aged 8 to 17 years recently diagnosed with Stage 3 T1D*.

**This indication is approved under accelerated approval based on evidence of reduced C-peptide decline. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).*

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of PA Health & Wellness® that Tziel is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Delayed Onset of Stage 3 Type 1 Diabetes (must meet all):

1. Diagnosis of Stage 2 T1D as evidenced by all of the following (a, b, and c):
 - a. Presence of 2 or more diabetes-related autoantibodies detected in 2 samples obtained within the last 6 months: anti-insulin autoantibodies (mIAA), islet cell antibodies (ICA), anti-glutamic acid decarboxylase(GAD)65ab, anti-ICA512ab, zinc transporter 8 autoantibody (ZnT8A), insulinoma-associated antigen 2 autoantibody (IA-2A);
 - b. Abnormal glucose tolerance during an oral glucose-tolerance test (OGTT) confirmed within the last 7 weeks (i, ii, or iii) (*two confirmatory tests are required for members age ≥ 18 years*):
 - i. Fasting plasma glucose ≥ 110 mg/dL, and < 126 mg/dL;
 - ii. 2 hour plasma glucose ≥ 140 mg/dL, and < 200 mg/dL;
 - iii. 30, 60, or 90 minute value on OGTT ≥ 200 mg/dL;
 - c. Member does not have symptoms of diabetes (e.g., polyuria, polydipsia, polyphagia);
2. Prescribed by or in consultation with an endocrinologist;
3. Age ≥ 1 year;
4. Member does not have a diagnosis of Stage 3 T1D or type 2 diabetes;
5. Documentation of member's current body surface area (BSA) (m^2);

6. Dose does not exceed a total of 11,240 mcg/m² administered over a 14-day treatment course (*see section V*).

Approval duration: 3 months (one 14-day treatment course only)

B. Delayed Progression of Recently Diagnosed Stage 3 Type 1 Diabetes (must meet all):

1. Diagnosis of Stage 3 T1D;
2. Diagnosis was made within the last 8 weeks;
3. Diagnosis is confirmed by one of the following (a-d)
 - a. A1c $\geq$ 6.5%
 - b. Fasting plasma glucose $\geq$ 126 mg/dL ($\geq$ 7.0 mmol/L);
 - c. 2-hour plasma glucose $\geq$ 200 mg/dL ($\geq$ 11.1 mmol/L) during oral glucose tolerance test;
 - d. Random plasma glucose $\geq$ 200 mg/dL ($\geq$ 11.1 mmol/L) during classic symptoms of hyperglycemia (e.g., polyuria, polydipsia, unexplained weight loss) or hyperglycemic crisis;
4. Prescribed by or in consultation with an endocrinologist;
5. Age 8 to 17 years;
6. Presence of 1 or more islet cell antibodies (ICA);
7. Peak C-peptide $\geq$ 0.2pmol/mL on a mixed-meal tolerance test;
8. Member has not been diagnosed with stage 4 T1D or type 2 diabetes;
9. Member has not previously received Tziel for Stage 2 T1D to delay the onset to Stage 3 T1D;
10. Member has not received two 12-day treatment courses of Tziel for Stage 3 T1D;
11. Documentation of member's current body surface area (BSA) (m²);
12. Dose does not exceed a total of 9,331 mcg/m² administered over a 12-day treatment course (*see section V*);
13. Request does not exceed a total of two 12-day treatment courses, administered approximately 6 months apart.

Approval duration: 12 months (two 12-day treatment courses only)

C. Other diagnoses/indications

1. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

II. Continued Therapy

A. All Indications

1. Continued therapy will not be authorized as Tziel is indicated to be administered as a one-time treatment course only.

Approval duration: Not applicable

B. Other diagnoses/indications (must meet 1 or 2):

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.PHARM.01) applies.

Approval duration: Duration of request or 6 months (whichever is less); or

2. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

III. Diagnoses/Indications for which coverage is NOT authorized:

- A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – PA.CP.PMN.53.
- B. Stage 3 or 4 T1D;
- C. Type 2 diabetes.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

BSA: body surface area

FDA: Food and Drug Administration

GAD: glutamic acid decarboxylase

IA-2A: insulinoma-associated antigen
2 autoantibody

ICA: islet cell antibodies

mIAA: anti-insulin autoantibodies

OGTT: oral glucose tolerance test

T1D: type 1 diabetes

ZnT8A: zinc transporter 8
autoantibody

Appendix B: Therapeutic Alternatives

Not Applicable

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): none reported
- Boxed warning(s): viral reactivation (Tzield is not recommended in patients with laboratory or clinical evidence of active Epstein-Barr virus and cytomegalovirus infection due to reports of serious, life-threatening cases of viral reactivation)

Appendix D: General Information

- There are 4 recognized stages of T1D:
 - Stage 1: single or transient single diabetes-related autoantibodies, normoglycemia, presymptomatic
 - Stage 2: ≥ 2 diabetes-related autoantibodies, dysglycemia, presymptomatic
 - Stage 3: ≥ 1 diabetes-related autoantibodies, hyperglycemia, symptomatic
 - Stage 4: longstanding T1D
- Treatment of T1D:
 - In 2010, teplizumab failed to meet the primary efficacy endpoint (a composite of total daily insulin usage and HbA1c level at 12 months) in the phase 3 Protégé study, demonstrating no difference compared to placebo for the treatment of patients with early-onset T1D; as a result, clinical programs were suspended.
 - A new phase 3 study for the treatment of early-onset T1D in children and adolescents with newly diagnosed disease (PROTECT, NCT03875729) was completed in 2023. Teplizumab met the primary end point of preservation of β -cell function as measured by stimulated C-peptide levels, but this did not translate to benefit with regard to the clinical outcomes; there were no significant differences compared to placebo for the

secondary end points of insulin doses that were required to meet glycemic goals, glycated hemoglobin levels, time in the target glucose range, and clinically important hypoglycemic events.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Delayed onset of Stage 3 T1D	14 day treatment course administered IV QD: - Day 1: 65 mcg/m² - Day 2: 125 mcg/m² - Day 3: 250 mcg/m² - Day 4: 500 mcg/m² - Days 5-14: 1,030 mcg/m²	11,240 mcg/m ² / treatment course
Stage 3 Type 1 Diabetes	- Day 1: 106 mcg/m² - Day 2: 425 mcg/m² - Day 3-12: 850 mcg/m²	9,331 mcg/m ² /treatment course

VI. Product Availability

Single-dose vial: 2 mg/2 mL

VII. References

1. Tziel Prescribing Information. Red Bank, NJ: Provention Bio, Inc; June 2026. Available at: <https://www.tziel.com>. Accessed June 23, 2026.
2. Insel RA, Dunne JL, Atkinson MA, et al. Staging presymptomatic type 1 diabetes: A scientific statement of JDRF, the Endocrine Society, and the American Diabetes Association. *Diabetes Care*. 2015; 38(10): 1964-1974.
3. Couper JJ, Haller MJ, Greenbaum CJ, et al. ISPAD clinical practice consensus guidelines 2018: Stages of type 1 diabetes in children and adolescents. *Pediatric Diabetes*. 2018; 19(S27): 20-27.
4. Mehta S, Ryabets-Lienhard A, Patel N, et al. Pediatric Endocrine Society statement on considerations for use of teplizumab (Tziel™) in clinical practice. *Horm Res Paediatr*. Published online April 30, 2024. DOI: 10.1159/000538775
5. Philip M, Achenbach P, Addala A, et al. Consensus guidance for monitoring individuals with islet autoantibody-positive pre-stage 3 type 1 diabetes. *Diabetes Care*. 2024; 47(8): 1276-1298.

Prevention of T1DM

6. Herold KC et al. An anti-CD3 antibody, teplizumab, in relatives at risk for type 1 diabetes. *New Engl J Med*. 2019; 381(7): 603-613. doi: 10.1056/NEJMoa1902226. Epub 2019 Jun 9. Erratum in: *N Engl J Med*. 2020 Feb 6; 382(6): 586.
7. Provention Bio, Inc. Teplizumab for prevention of type 1 diabetes in relatives "at-risk". Available at: <https://clinicaltrials.gov/ct2/show/NCT01030861>. Accessed November 6, 2024.
8. Sims EK et al. Teplizumab improves and stabilizes beta cell function in antibody-positive high-risk individuals. *Science Translational Medicine*. 2021; 13(583): eabc8980.

Treatment of T1DM

9. Sherry N et al. Teplizumab for treatment of type 1 diabetes (Protégé study): 1-year results from a randomized, placebo-controlled trial. *Lancet*. 2011; 378(9790): 487-497.

10. Hagopian W et al. Teplizumab preserves C-peptide in recent-onset type 1 diabetes: two-year results from the randomized, placebo-controlled Protégé trial. *Diabetes*. 2013; 62(11): 3901-3908.
11. Herold KC et al. Teplizumab (anti-CD3 mAb) treatment preserves C-peptide responses in patients with new-onset type 1 diabetes in a randomized controlled trial: Metabolic and immunologic features at baseline identify a subgroup of responders. *Diabetes*. 2013; 62: 3766-3774.
12. Provention Bio, Inc. Recent-onset type 1 diabetes trial evaluating efficacy and safety of teplizumab (PROTECT). Available at: <https://clinicaltrials.gov/ct2/show/NCT03875729>. Accessed October 19, 2023.
13. Nourelden AZ et al. Safety and efficacy of teplizumab for treatment of type one diabetes mellitus: A systematic review and meta-analysis. *Endocr Metab Immune Disord Drug Targets*. 2021; 21(10): 1895-1904.
14. Ramos EL, Dayan CM, Chatenoud L, et al. Teplizumab and β -cell function in newly diagnosed type 1 diabetes. *N Engl J Med*. 2023; 289: 2151-2161.

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

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

Reviews, Revisions, and Approvals	Date
Policy created	01/2023
1Q 2024 annual review: added HCPCS code [J9381] and deleted HCPCS code [C9399] and HCPCS code [J3590]; updated Appendix D; references reviewed and updated.	01/2024
1Q 2025 annual review: added ZnT8A and IA-2A as additional diabetes-related autoantibody options per pivotal study design and specialist feedback; added information about PROTECT trial to Appendix D; references reviewed and updated.	01/2025
1Q 2026 annual review: no significant changes; references reviewed and updated	01/2026
RT4: revised age requirement from ≥ 8 years to ≥ 1 year to reflect pediatric extension and added new boxed warning (viral reactivation) per updated prescribing information.	05/2026