Teplizumab-mzwv (Tzield)

- Clinical Policy Bulletins
- Medical Clinical Policy Bulletins

Number: 1022

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Policy

Scope of Policy

This Clinical Policy Bulletin addresses teplizumab-mzwv (Tzield) for commercial medical plans. For Medicare criteria, see Medicare Part B Criteria.

Note: Requires Precertification:

Precertification of teplizumab-mzwv (Tzield) is required of all Aetna participating providers and members in applicable plan designs. For precertification of teplizumab-mzwv (Tzield), call (866) 752-7021, or fax (888) 267-3277. For Statement of Medical Necessity (SMN) precertification forms, see Specialty Pharmacy Precertification.

1. **Prescriber Specialties**

   This medication must be prescribed by or in consultation with an endocrinologist.

2. **Criteria for Initial Approval**

   Aetna considers teplizumab-mzwv (Tzield) medically necessary for members with Stage 2 type 1 diabetes to delay the onset of Stage 3 type 1 diabetes when *all* of the following criteria are met:

   1. Member is 8 years of age and older; *and*
   2. Member has two or more of the following pancreatic islet cell autoantibodies detected in two samples obtained within the past 6 months:

      1. Glutamic acid decarboxylase 65 (GAD) autoantibodies
      2. Insulin autoantibody (IAA)
      3. Insulinoma-associated antigen 2 autoantibody (IA-2A)
      4. Zinc transporter 8 autoantibody (ZnT8A)
      5. Islet cell autoantibody (ICA); *and*

   3. Member has an abnormal oral glucose tolerance test (OGTT) confirming dysglycemia within the past 2 months when *any* of the following are met:

      1. Fasting blood glucose level of 100 to 125 mg/dL (5.6 to 6.9 mmol/L); *or*
      2. 2-hour postprandial plasma glucose level of at least 140 mg/dL (7.8 mmol/L) and less than 200 mg/dL (11.1 mmol/L); *or*
      3. Intervening postprandial glucose level at 30, 60, or 90 minutes of greater than 200 mg per deciliter (11.1 mmol/L) on two occasions; *and*

   4. Member does not have symptoms associated with type 1 diabetes (e.g., increased urination, excessive thirst, weight loss); *and*
   5. Member will not exceed a one-time 14-day treatment course consisting of the following dosing schedule:

      1. Day 1: 65 mcg/m^2

2. Day 2: 125 mcg/m^2
3. Day 3: 250 mcg/m^2
4. Day 4: 500 mcg/m^2
5. Days 5 through 14: 1,030 mcg/m^2

Aetna considers all other indications as experimental, investigational, or unproven.

3. **Related Policies**

1. CPB 0070 - Diabetes Tests, Programs and Supplies
2. CPB 0587 - Pancreas Kidney Transplantation
3. CPB 0601 - Pancreas Transplantation Alone (PTA) and Islet Cell Transplantation
4. CPB 0742 - Intermittent Intravenous Insulin Therapy

Dosage and Administration

Teplizumab-mzwv is available as Tzield and supplied as a 2 mg per 2 mL (1 mg/mL) single-dose vial for intravenous use. Below includes dosing and administration recommendations as per the FDA-approved prescribing information:

- Tzield is indicated for adult and pediatric persons 8 years of age and older who have a diagnosis of Stage 2 type 1 diabetes.
- Confirm Stage 2 type 1 diabetes by documenting at least two positive pancreatic islet autoantibodies in those who have dysglycemia without overt hyperglycemia using an oral glucose tolerance test (OGTT) or alternative method if appropriate and OGTT is not available.
- In persons who meet criteria for a diagnosis of Stage 2 type 1 diabetes, ensure the clinical history of the individual does not suggest type 2 diabetes.
- Prior to initiating Tzield, obtain a complete blood count and liver enzyme tests. Use of Tzield is not recommended in persons with certain laboratory abnormalities.
- Must dilute Tzield in 0.9% Sodium Chloride Injection, USP. See full prescribing information for detailed preparation and administration instructions.
- Premedicate with:
    - a nonsteroidal anti-inflammatory drug (NSAID) or acetaminophen,
    - an antihistamine, and/or
    - an antiemetic before each Tzield dose for at least the first 5 days of the 14-day treatment course.
- Administer Tzield by intravenous infusion (over a minimum of 30 minutes), using a body surface area-based dosing, once daily for 14 consecutive days as follows:
    - 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

  Do not administer two doses on the same day.

Source: Provention Bio, 2023

CPT Codes / HCPCS Codes / ICD-10 Codes

Other CPT codes related to the CPB:

Code	Code Description
80076	Hepatic function panel

Code	Code Description
82947	Glucose; quantitative, blood (except reagent strip)
82948	blood, reagent strip
82950	post glucose dose (includes glucose)
82951	tolerance test (GTT), 3 specimens (includes glucose)
82952	tolerance test, each additional beyond 3 specimens (List separately in addition to code for primary procedure)
82962	Glucose, blood by glucose monitoring device(s) cleared by the FDA specifically for home use
85027	Blood count; complete (CBC), automated (Hgb, Hct, RBC, WBC and platelet count)
86337	Insulin antibodies
86341	Islet cell antibody
96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
96413	Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug
99601	Home infusion/specialty drug administration, per visit (up to 2 hours)
99602	each additional hour (List separately in addition to code for primary procedure)

HCPCS codes covered if selection criteria are met:

J9381	Injection, teplizumab-mzwv, 5 mcg

Other HCPCS codes related to the CPB:

A4216	Sterile water, saline and/or dextrose, diluent/flush, 10 ml

ICD-10 codes covered if selection criteria are met:

E10.10 – E10.9	Type 1 diabetes mellitus

Background

U.S. Food and Drug Administration (FDA)-Approved Indications

- Tzield is indicated to delay the onset of Stage 3 type 1 diabetes in adults and pediatric patients 8 years of age and older with Stage 2 type 1 diabetes.

Teplizumab-mzwv, branded as Tzield (Provention Bio, Inc.), is a CD3-directed antibody that binds to certain immune system cells (i.e., CD3, which is a cell surface antigen present on T lymphocytes) and delays progression to Stage 3 type 1 diabetes in patients aged 8 years and older with Stage 2 type 1 diabetes. Teplizumab-mzwv may deactivate the immune cells that attack insulin-producing cells, while increasing the proportion of cells that help moderate the immune response. Specifically, the mechanism may involve partial agonistic signaling and deactivation of pancreatic beta cell autoreactive T lymphocytes, and leads to an increase in the proportion of regulatory T cells and of exhausted CD8+ T cells in peripheral blood. Tzield is administered by intravenous infusion once daily for 14 consecutive days (FDA, 2022; Provention Bio, 2023).

Although teplizumab-mzwv does not have any specified contraindications, the label does include the following warnings and precautions: cytokine release syndrome (CRS), serious infections, lymphopenia, and hypersensitivity reactions. In clinical trials, CRS was reported in 5 percent of teplizumab-treated patients compared to 0.8 percent of control-treated patients during the treatment period and through 28 days after the last study drug administration. Teplizumab-treated patients had a higher rate of serious infections (3.5 percent) than control-treated patients (2 percent), including gastroenteritis, cellulitis, pneumonia, abscess, and sepsis. Seventy-eight percent of teplizumab-treated patients developed lymphopenia compared to 11 percent of control-treated patients. Acute hypersensitivity reactions including serum sickness, angioedema, urticaria, rash, vomiting and bronchospasm occurred in teplizumab-treated patients.

The safety of immunization with live-attenuated vaccines in teplizumab-treated patients has not been studied. Additionally, teplizumab may interfere with the immune response to vaccination and decrease vaccine efficacy. It is recommended that all age-appropriate vaccinations be administered prior to starting Tzield.

Available case reports from clinical trials are insufficient to identify a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. Although there are no data on teplizumab-mzwv, monoclonal antibodies can be

actively transported across the placenta, and may cause immunosuppression in the utero-exposed infant. To minimize exposure to a fetus, avoid use of teplizumab-mzwv during pregnancy and at least 30 days prior to planned pregnancy. There are no data on the presence of teplizumab-mzwv in either human or animal milk, the effects on the breastfed child, or the effects on milk production. A lactating woman may consider pumping and discarding breast milk during and for 20 days after Tzield administration.

Clinical studies of teplizumab-mzwv to delay the onset of Stage 3 type 1 diabetes did not include patients 65 years of age and older.

The most common adverse reactions (greater than 10 percent) include lymphopenia, rash, leukopenia and headache.

Type 1 Diabetes

Type 1 diabetes (T1D), or type 1 diabetes mellitus (T1DM), is a chronic autoimmune disease in which there is an immune-mediated loss of functional pancreatic beta cells resulting in symptomatic diabetes and lifelong dependence on exogenous insulin for survival (Insel et al, 2015). Although it can appear at any age, T1D diabetes is usually diagnosed in children and young adults. There is no cure and current treatment has been directed towards glucose management via insulin, diet and lifestyle measures to prevent complications.

Beta cells are a type of islet of Langerhan cell in the pancreas that produce the hormone insulin, which the body uses to facilitate glucose to enter cells for energy production. In T1D, the pancreas will produce little or no insulin, and represents a disease continuum that begins prior to its symptomatic manifestations. T1D is characterized by four stages (Couper et al, 2018, Insel et al, 2015, Levitsky and Misra, 2022):

- Stage 1: Beta cell autoimmunity (2 or more islet autoantibodies), normal blood glucose (normoglycemic), and pre-symptomatic
- Stage 2: Beta cell autoimmunity (2 or more islet autoantibodies), raised blood glucose (dysglycemia), and pre-symptomatic
- Stage 3: Beta cell (islet) autoimmunity, raised blood glucose (dysglycemia), and symptomatic
- Stage 4 Long standing T1DM.

In genetically susceptible persons, T1D progresses through asymptomatic stages before the development of overt hyperglycemia (Herold et al, 2019). Insel and colleagues (2015) state that "Stage 2, like stage 1, includes individuals with two or more islet autoantibodies but whose disease has now progressed to the development of glucose intolerance, or dysglycemia, from loss of functional β-cell mass. The 5-year risk of symptomatic disease at this stage is approximately 75%, and the lifetime risk approaches 100%. Stage 3 represents manifestations of the typical clinical symptoms and signs of diabetes, which may include polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis (DKA), and others". Couper et al (2018) state, "The majority of children at risk of type 1 diabetes with multiple islet antibodies progress to diabetes within the next 15 years, compared to ~10% who have a single islet antibody".

Herold et al (2019) state that Fc receptor–nonbinding anti-CD3 monoclonal antibodies, such as teplizumab, reduces the loss of (delaying the decline in) beta cell function in patients diagnosed with recent-onset clinical T1D. The authors conducted a phase 2, randomized, placebo-controlled, double-blind trial (NCT01030861) of teplizumab involving relatives of patients with T1D who did not have diabetes but were at high risk for development of clinical disease. Patients (n=76; ages 8 to 49 years) were randomly assigned to a single 14-day course of teplizumab or placebo, and follow-up for progression to clinical T1D was performed with the use of oral glucose-tolerance tests (OGTT) at 6-month intervals. Of the total participants (55 of whom were 18 years of age or younger), 44 were randomized to the teplizumab group and 32 to the placebo group. The authors found that the median time to the diagnosis of T1D was 48.4 months in the teplizumab group and 24.4 months in the placebo group; the disease was diagnosed in 19 (43%) of the participants who received teplizumab and in 23 (72%) of those who received placebo. The hazard ratio for the diagnosis of type 1 diabetes (teplizumab vs. placebo) was 0.41 (p= 0.006). The annualized rates of diagnosis of diabetes were 14.9% per year in the teplizumab group and 35.9% per year in the placebo group. There were expected adverse events of rash and transient lymphopenia. KLRG1+TIGIT+CD8+ T cells were more common in the teplizumab group than in the placebo group. Among the participants who were HLA-DR3–negative, HLA-DR4–positive, or anti–zinc transporter 8 antibody–negative, fewer participants in the teplizumab group than in the placebo group had diabetes diagnosed. The authors concluded that teplizumab delayed progression to clinical T1D in high-risk participants. The authors point out certain study limitations such as the cohort was relatively small, and the estimated power was limited. The trial population was overwhelmingly made up of non-Hispanic white participants. The drug was given for only one course, and although repeated dosing may provide additional benefits and capture more persons with active disease or prolong the therapeutic effect, this strategy was not tested in this trial.

In November 2022, the FDA announced the approval of the first drug that can delay the onset of T1D. The FDA approved Tzield (teplizumab-mzwv) injection to delay the onset of stage 3 type 1 diabetes in adults and pediatric patients 8 years and older who currently have stage 2 type 1 diabetes. The approval is based on the safety and efficacy that was evaluated in the *Teplizumab for Prevention of Type 1 Diabetes In Relatives "At-Risk"* study (NCT01030861). Stage 2 type 1 diabetes was defined as having both of the following:

- Two or more of the following pancreatic islet autoantibodies:

    - Glutamic acid decarboxylase 65 (GAD) autoantibodies
    - Insulin autoantibody (IAA)
    - Insulinoma-associated antigen 2 autoantibody (IA-2A)
    - Zinc transporter 8 autoantibody (ZnT8A)
    - Islet cell autoantibody (ICA); and

- Dysglycemia on oral glucose tolerance testing (OGTT)

The trial results showed that over a median follow-up of 51 months, 45% of the 44 patients who received Tzield were later diagnosed with stage 3 type 1 diabetes, compared to 72% of the 32 patients who received a placebo. The mid-range time from randomization to stage 3 type 1 diabetes diagnosis was 50 months for the patients who received Tzield and 25 months for those who received a placebo. Per the FDA, this represents a statistically significant delay in the development of stage 3 type 1 diabetes. Thus, Tzield received Priority Review and Breakthrough Therapy designations for this indication.

Per the American Diabetes Association (ADA) “Standards of Care in Diabetes-2024”, staging of type 1 diabetes stage 2 diagnostic criteria includes the following:

- Islet autoantibodies (usually multiple);
- Fasting blood glucose level of 100 to 125 mg/dl (5.6 to 6.9 mmol/L);
- 2-hour plasma glucose140 to 199 mg/dl (7.8 to 11 mmol/L);
- A1C 5.7 to 6.4% (39 to 47 mmol/mol) or greater than or equal to 10% increase in A1C.

References

The above policy is based on the following references:

1. American Diabetes Association Professional Practice Committee. 2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes-2024. Diabetes Care. 2024;47(Suppl 1):S20-S42.
2. Couper JJ, Haller MJ, Greenbaum CJ, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Stages of type 1 diabetes in children and adolescents. Pediatr Diabetes. 2018;19 Suppl 27:20-27.
3. Herold KC, Bundy BN, Long SA, et al. An Anti-CD3 antibody, teplizumab, in relatives at risk for type 1 diabetes. N Engl J Med 2019; 381:603-613.
4. 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.
5. Levitsky LL, Misra M. Epidemiology, presentation, and diagnosis of type 1 diabetes mellitus in children and adolescents. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed June 2022.
6. Provention Bio, Inc. Tzield (teplizumab-mzwv) injection, for intravenous use. Prescribing Information. Red Bank, NJ: Provention Bio; revised December 2023.
7. U.S. Food and Drug Administration (FDA). FDA approves first drug that can delay onset of type 1 diabetes. Press Release. Silver Spring, MD: FDA; November 17, 2022.

Policy History

- Last Review 08/29/2024

  Effective: 03/17/2023

  Next Review: 06/22/2025

- Review History
- Definitions

Additional Information

- Clinical Policy Bulletin Notes