Drug Coverage Policy

Effective Date.....4/15/2024
Coverage Policy Number.....IP0537

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 and have discretion in making individual coverage determinations. 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.

Medical Necessity Criteria

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

1. **Type 1 Diabetes (Clinical/Stage 3), Delay of Onset.** Individual meets **ALL** of the following criteria:
    A. Age 8 years or older
    B. Documentation of at least **TWO** of the following type 1 diabetes-related autoantibodies on two separate occasions:
        i. anti-glutamic acid decarboxylase 65
        ii. anti-islet antigen-2
        iii. islet-cell autoantibody

iv. micro insulin
v. anti-zinc transporter 8

C. Documentation of **EITHER** of the following:
   i. Oral glucose tolerance test (OGTT)
      (1) **EITHER** of the following:
         a. Results of OGTT indicate dysglycemia as evidenced by **ONE** of the following:
            i. Fasting plasma glucose level greater than or equal to 100 and less than or equal to 125 mg/dL
            ii. Two-hour postprandial plasma glucose level greater than or equal to 140 and less than 200 mg/dL
            iii. Intervening postprandial glucose level at 30, 60 or 90 minutes greater than 200 mg/dL
         b. 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.
   ii. A1C 5.7-6 to less than 6.5% in the preceding 2 months
D. Does **NOT** have stage 3 type 1 diabetes mellitus (no clinical symptoms, not receiving treatment, failed OGTT)
E. Prescriber attests to **ALL** of the following:
   i. Adequate hematologic function
   ii. Adequate hepatic function
   iii. Does **NOT** have evidence of acute infection with Epstein-Barr Virus or cytomegalovirus
   iv. Does **NOT** have active serious infection
F. Has **NOT** received Tzield in the past
G. Medication is prescribed by an endocrinologist

Dosing. A one-time, 14-day course of Tzield with the following regimen:
1. 65 mcg/m2 body surface area (BSA) given intravenously on Day 1;
2. 125 mcg/m2 BSA given intravenously on Day 2;
3. 250 mcg/m2 BSA given intravenously on Day 3;
4. 500 mcg/m2 BSA given intravenously on Day 4;
5. 1,030 mcg/m2 BSA given intravenously once daily on Days 5 through 14.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Reauthorization Criteria

Not applicable for continuation beyond initial approval duration.

Authorization Duration

Authorization is for a one-time approval, 14-day course.

Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

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 individuals with a diagnosis of clinical type 1 diabetes (i.e., Stage 3 type 1 diabetes).

2. **Type 2 Diabetes.** Tzield is not indicated for individuals with a diagnosis of type 2 diabetes.

Background

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 (2023) 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.[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).

According to the ADA Standards, three distinct stages of type 1 diabetes can be identified, which serve as a framework for future research and regulatory decision-making.[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 involve 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, glycemia is normal. 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.

References

1. Tzield intravenous infusion [prescribing information]. Red Bank, NJ: Provention; November 2022.
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 – 2023. *Diabetes Care*. 2023;46(Suppl 1):S1-S291.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	• Updated coverage policy title.	04/01/2024

	• 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.	

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