teplizumab-mzwv (Tzield™)

Medicare Advantage Medical Policy #MA-064
Original Effective Date: 02/01/2025
Current Effective Date: 02/01/2025

Applies to all products administered or underwritten by the Health Plan, unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Health Plan may consider teplizumab-mzwv (Tzield™)‡ for patients with Stage 2 type 1 diabetes to delay the onset of Stage 3 type 1 diabetes to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for teplizumab-mzwv (Tzield) will be considered when the following criteria are met:

- Patient has stage 2 type 1 diabetes; AND
  (Note: Stage 2 Type 1 diabetes is characterized by the presence of beta cell autoantibodies and presymptomatic dysglycemia, which includes impaired fasting glucose or impaired glucose tolerance without diabetic range hyperglycemia.)
- Patient is 8 years of age or older; AND
- 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.)*
- Patient does NOT have type 2 diabetes; AND
- Patient has tested positive for at least TWO of the following type 1 diabetes-related autoantibodies: anti-glutamic acid decarboxylase 65 (anti-GAD65); anti-islet antigen-2 (anti-IA-2); islet-cell autoantibody (ICA); micro insulin; anti-zinc transporter 8 (anti-ZnT8); AND
- Patient has evidence of dysglycemia without overt hyperglycemia as evidenced by ONE of the following:
  - Fasting plasma glucose level ≥ 100 to < 126 mg/dL; OR
  - 2-hour postprandial plasma glucose level ≥ 140 to < 200 mg/dL; OR
  - Intervening postprandial glucose level at 30, 60, or 90 minutes > 200 mg/dL; OR
  - HbA1c ≥ 5.7 to < 6.5% (5.7-6.4%); AND
- Patient does not have evidence of hematologic compromise, which defined by meeting ALL of the following:
  - Lymphocyte count ≥ 1,000 lymphocytes/µL; AND

  - Hemoglobin ≥ 10 g/dL; AND
  - Platelet count ≥ 150,000 platelets/µL; AND
  - Absolute neutrophil count ≥ 1,500 neutrophils/µL; AND
- Patient does not have evidence of hepatic compromise, which is defined by meeting ALL of the following:
  - Alanine aminotransferase (ALT) ≤ 2 times the upper limit of normal (ULN); AND
  - Aspartate aminotransferase (AST) ≤ 2 times the ULN; AND
  - Bilirubin ≤ 1.5 times the ULN; AND
- According to the prescriber, the patient does NOT have ANY of the following:
  - Laboratory or clinical evidence of acute infection with Epstein-Barr Virus or cytomegalovirus; AND
  - Active serious infection; AND
  - Chronic active infection (other than localized skin infection); AND
- Patient has NOT received a full course of or started a course of Tzield in the past; AND
- The requested dose is 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
  - Day 5-14: 1,030 mcg/m^2

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Health Plan considers the use of teplizumab-mzwv (Tzield) for any non-FDA approved indication to be **investigational.***

Background/Overview

Tzield is a CD3-directed antibody indicated to delay the onset of Stage 3 type 1 diabetes in adults and pediatric patients aged 8 years and older with Stage 2 type 1 diabetes. It is available as a 2 mg per 2 ml single dose vial and is to be administered once daily by intravenous infusion for 14 consecutive days. Baseline laboratory testing is required prior to initiating therapy with Tzield. Pre-medication with a non-steroidal anti-inflammatory drug or acetaminophen, an antihistamine, and/or an antiemetic before each Tzield dose is recommended for the first 5 days of therapy.

Type 1 diabetes is an autoimmune disease in which insulin-producing beta cells in the pancreas are destroyed. Clinically evident type 1 diabetes is referred to as Stage 3 type 1 diabetes. It is characterized by new-onset hyperglycemia and presence of symptoms. Diagnostic criteria involve one of the following: fasting plasma glucose ≥ 126 mg/dL, 2-hour postprandial glucose ≥ 200 mg/dL during an OGTT (75 grams), HbA1C ≥ 6.5%, or random plasma glucose ≥ 200 mg/dL for a patient

with classic symptoms of hyperglycemia or hyperglycemic crisis. Pre-symptomatic states include Stage 1 type 1 diabetes and Stage 2 type 1 diabetes. In Stage 1 disease, glycemia is normal, and in Stage 2 disease, dysglycemia is present but below the threshold considered overt or Stage 3 type 1 diabetes. Type 1 diabetes is often not diagnosed until Stage 3 disease develops. Patients who have a relative that has a diagnosis of type 1 diabetes are at greater risk of developing type 1 diabetes themselves. The American Diabetes Association (ADA) recommends screening for autoantibodies in patients with first-degree relatives with type 1 diabetes. The presence of multiple antibodies confers high probability of disease progression, but often does not predict the timing of when disease progression will occur. Eventually, all patients who are diagnosed with type 1 diabetes will have to monitor blood sugar levels and require insulin replacement to survive.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Tzield was approved in November of 2022 and is indicated to delay the onset of Stage 3 type 1 diabetes in adults and pediatric patients aged 8 years and older with Stage 2 type 1 diabetes.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The effectiveness of Tzield was investigated in a randomized, double-blind, event-driven, placebo-controlled study (Study 1) in 76 patients, 8 to 49 years of age with Stage 2 type 1 diabetes. Stage 2 type 1 diabetes was defined as having both of the following:

1. 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)
2. Dysglycemia on oral glucose tolerance testing

In this study, patients were randomized to receive Tzield or placebo once daily by intravenous infusion for 14 days. Patients in the Tzield group had a total drug exposure that was comparable to the total drug exposure achieved with the recommended total Tzield dosage. The primary efficacy endpoint in this study was the time from randomization to development of Stage 3 type 1 diabetes diagnosis.

In Study 1, Stage 3 type 1 diabetes was diagnosed in 20 (45%) of the Tzield-treated patients and in 23 (72%) of the placebo-treated patients. A Cox proportional hazards model, stratified by age and oral glucose tolerance test status at randomization, demonstrated that the median time from randomization to Stage 3 type 1 diabetes diagnosis was 50 months in the Tzield group and 25 months in the placebo group, for a difference of 25 months. With a median follow-up time of 51 months, therapy with Tzield resulted in a statistically significant delay in the development of Stage 3 type 1 diabetes, hazard ratio 0.41 (95% CI: 0.22 to 0.78; p=0.0066).

References

1. Tzield [package insert]. Provention Bio, Inc. Red Bank, New Jersey. November 2022.
2. Tzield (teplizumab-mzwv intravenous infusion – Provention). Drug Evaluation. Express Scripts. January 2023.
3. Tzield (teplizumab-mzwv). New Drug Review. IPD Analytics. Published December 2022.

Policy History

Original Effective Date: 02/01/2025
Current Effective Date: 02/01/2025
11/19/2024 UM Committee review. New policy.
Next Scheduled Review Date: 11/2025

Coding

The five character codes included in the Health Plan Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2023 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of the Health Plan Medical Policy Coverage Guidelines is with the Health Plan and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in the Health Plan Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of the Health Plan Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J9381
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the Health Plan Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Health Plan recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

Medicare Advantage Members

Established coverage criteria for Medicare Advantage members can be found in Medicare coverage guidelines in statutes, regulations, National Coverage Determinations (NCD)s, and Local Coverage Determinations (LCD)s. To determine if a National or Local Coverage Determination addresses coverage for a specific service, refer to the Medicare Coverage Database at the following link: https://www.cms.gov/medicare-coverage-database/search.aspx. You may wish to review the Guide to the MCD Search here: https://www.cms.gov/medicare-coverage-database/help/mcd-bene-help.aspx.

When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, internal coverage criteria may be developed. This policy is to serve as the summary of evidence, a list of resources and an explanation of the rationale that supports the adoption of this internal coverage criteria.