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Teplizumab-mzwv

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Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted

study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Teplizumab-mzwv (Tzield®) **may be considered medically necessary** when **ALL** the following criteria are met:

1. Adult and pediatric individuals ≥ 8 years of age;
2. Stage 2 type 1 diabetes, confirmed by:
    a. At least two positive pancreatic islet cell autoantibodies, and
    b. Dysglycemia without overt hyperglycemia using an oral glucose tolerance test (if an oral glucose tolerance test is not available, an alternative method for diagnosing dysglycemia without overt hyperglycemia may be appropriate);
3. Clinical history of the individual does not suggest type 2 diabetes; AND
4. Individual does **NOT** have any of the following:
    a. Lymphocyte count less than 1,000 lymphocytes/mcL.
    b. Hemoglobin less than 10 g/dL.
    c. Platelet count less than 150,000 platelets/mcL.
    d. Absolute neutrophil count less than 1,500 neutrophils/mcL.
    e. Elevated ALT or AST greater than 2 times the upper limit of normal (ULN) or bilirubin greater than 1.5 times ULN.
    f. Laboratory or clinical evidence of acute infection with Epstein-Barr virus (EBV) or cytomegalovirus (CMV), and
    g. Active serious infection or chronic active infection other than localized skin infections.

Teplizumab-mzwv (Tzield®) is **considered experimental, investigational, and/or unproven** for all other indications or when used as a repeat course of treatment (beyond the initial 14 doses).

Policy Guidelines

None.

Description

Diabetes Mellitus

Diabetes mellitus (DM) is a disease of abnormal glucose metabolism caused by either a deficiency of insulin or resistance to insulin, resulting in elevated blood glucose levels. The American Diabetes Association (ADA) Standards of Medical Care in Diabetes (2023) notes diabetes can be classified into general categories: Type 1 (due to autoimmune β-cell destruction, usually leading to absolute insulin deficiency, including latent autoimmune

diabetes of adulthood), Type 2 diabetes (due to a progressive loss of adequate β-cell insulin secretion frequently on the background of insulin resistance and metabolic syndrome), gestational diabetes mellitus (GDM) (diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes prior to gestation), and specific types of diabetes due to other causes. They also note the traditional paradigms of Type 2 diabetes occurring only in adults and Type 1 diabetes (T1D) only in children are no longer accurate, as both diseases occur in both age-groups. (1)

Symptoms

Children with T1D often present with the hallmark symptoms of polyuria/polydipsia, and approximately half present with diabetic ketoacidosis (DKA). The onset of T1D in adults may be more variable; they may not present with the classic symptoms seen in children and may experience temporary remission from the need for insulin. The features most useful in discrimination of type 1 diabetes include younger age at diagnosis (<35 years) with lower body mass index (BMI) (<25 kg/m^2), unintentional weight loss, ketoacidosis, and glucose >360 mg/dL (20 mmol/L) at presentation. The ADA states it is important to realize the classification of diabetes type is not always straightforward and that misdiagnosis is common (e.g., adults with type 1 diabetes misdiagnosed as having type 2 diabetes; individuals with maturity-onset diabetes of the young [MODY] misdiagnosed as having type 1 diabetes, etc.). (1)

Dysglycemia refers to an abnormality in blood sugar stability. This can include hypoglycemia (low blood sugar) or hyperglycemia (high blood sugar). Individuals with hypoglycemia may experience fatigue, paleness, irritability, sweating, shakiness, anxiety, or heart palpitations. When blood sugar levels are extremely low, it can cause slurring of words as well as seizures and loss of consciousness. Hyperglycemia only causes symptoms when the blood sugar levels are significantly elevated. These symptoms tend to develop gradually and worsen the longer the blood sugar remains elevated. Symptoms may include increased thirst, frequent urination, blurred vision, headache, fatigue, dry mouth, weakness, confusion, nausea and vomiting; and when left untreated, it can lead to coma.

Staging

The persistent presence of two or more islet autoantibodies is a near certain predictor of clinical diabetes. The rate of progression is dependent on the age at first detection of autoantibody, number of autoantibodies, autoantibody specificity, and autoantibody titer. Glucose and A1C levels rise well before the clinical onset of diabetes, making diagnosis feasible well before the onset of DKA. Three distinct stages of type 1 diabetes can be identified (Table 1) and serve as a framework for future research and regulatory decision-making according to the ADA. (1)

Table 1. Staging of Type 1 Diabetes

	Stage 1	**Stage 2**	**Stage 3**
Characteristics	• Autoimmunity • Normoglycemia • Presymptomatic	• Autoimmunity • Dysglycemia • Presymptomatic	• Autoimmunity • Overt hyperglycemia

			• Symptomatic
Diagnostic Criteria	• Multiple islet autoantibodies • No IGT or IFG	• Islet autoantibodies (usually multiple) • Dysglycemia: IGF and/or IGT • FPG 100-125 mg/dL (5.6-6.9 mmol/L) • 2-h PG 140-199 mg/dL (7.8-11.0 mmol/L) • A1C 5.7-6.4% (39-47 mmol/mol) or ≥10% increase in A1C	• Autoantibodies may become absent • Diabetes by standard criteria

IGT: impaired glucose tolerance; IFG: impaired fasting glucose; FPG: fasting plasma glucose; 2-h PG: 2-hour plasma glucose; mg/dL: milligram per deciliter; mmol/L: millimoles per liter; mmol/mol: millimoles per mole; A1C: hemoglobin A1C.

Immunologic

Like many autoimmune diseases, type 1 diabetes usually has a relapsing, remitting disease course with autoantibody and T cellular responses to islet autoantigens that precede the clinical onset of the disease process. The immunologic diagnosis of autoimmune diseases relies primarily on the detection of autoantibodies directed to islet autoantigens in the serum of type 1 diabetic individuals. Although their pathogenic significance remains uncertain, they have the practical advantage of serving as surrogate biomarkers for predicting the clinical onset of type 1 diabetes. Individuals with multiple islet autoantibodies with normoglycemia are considered to be at stage 1 type 1 diabetes, those with multiple islet autoantibodies and dysglycemia are at stage 2 type 1 diabetes, and those who developed the clinical symptoms of type 1 diabetes are stage 3. (2)

Autoantibodies

Several clinically useful serum autoantibodies can be detected during the preclinical phase of type 1 diabetes, including islet cell antibodies (ICA), insulin autoantibodies (IAA), antibodies to glutamic acid decarboxylase (GAD), antibodies to tyrosine phosphatase-like proteins such as insulinoma-associated protein (IA-2, ICA512), and antibodies to the zinc transporter 8 (ZnT8). Sixty to 80 percent of patients with newly diagnosed type 1 diabetes have ZnT8 autoantibodies. In addition, 26 percent of subjects with antibody negative (insulin, GAD, IA-2, and ICA) type 1 diabetes have ZnT8 autoantibodies. In addition to identifying children at risk for type 1 diabetes, the presence of ICA and GAD antibodies can also identify late-onset type 1 diabetes in adults thought to have type 2 diabetes. (2, 3, 4)

Treatment Options

Current treatment options for individuals with type 1 diabetes include intensive insulin therapy and glucose monitoring, along with appropriate diabetes education and lifestyle management which includes nutrition therapy. Intensive insulin therapy consists of delivering insulin using one of two methods: multiple (3-4 per day) daily injections of insulin, which combine rapid and

long-acting insulin analogues; or continuous subcutaneous insulin infusion (i.e., insulin pump), which provides rapid-acting insulin through a catheter that is inserted into subcutaneous tissue of the anterior abdominal wall. Newly diagnosed individuals usually start with a regimen of multiple daily injections; some may transition to continuous subcutaneous insulin infusions later. (4)

Regulatory Status
Teplizumab-mzwv (Tzield®) is a CD3-directed antibody approved by the U.S. Food and Drug Administration (FDA) in November 2022 to delay the onset of stage 3 type 1 diabetes in adult and pediatric patients 8 years of age and older with stage 2 type 1 diabetes. (5)

Rationale

This medical policy was developed in 2022 and is based on the clinical studies provided to the U.S. Food and Drug Administration (FDA) for approval and a literature search of the PubMed database as of February 22, 2024.

Teplizumab (5)
The effectiveness of Tzield was investigated in a randomized, double-blind, event-driven, placebo-controlled study (Study TN-10; NCT01030861) 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:
    a. Glutamic acid decarboxylase 65 (GAD) autoantibodies;
    b. Insulin autoantibody (IAA);
    c. Insulinoma-associated antigen 2 autoantibody (IA-2A);
    d. Zinc transporter 8 autoantibody (ZnT8A);
    e. 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.

Baseline Patient Characteristics
In this study, 45% were female; 97% White, 1% Asian, and 1% reported multiracial background; 3% were Hispanic or Latino ethnicity; and 95% were from the United States. The median age was 14 years (72% were <18 years old). See Table 2.

Table 2. Baseline Age Characteristics of Adults and Pediatric Patients 8 Years of Age and Older with Stage 2 Type 1 Diabetes (Study TN-10)[a]

	Tzield N=44	Placebo N=32

Age Group		
≥18 years	34%	19%
<18 years	66%	81%
Pediatric Age Group Quartiles		
8 to <11 years	21%	25%
11 to <14 years	27%	31%
14 to <18 years	18%	25%

[a] Intent to treat (ITT) population

Baseline Disease Characteristics

Table 3 displays the baseline disease characteristics in Study TN-10.

Table 3. Baseline Disease Characteristics of Adults and Pediatric Patients 8 Years of Age and Older with Stage 2 Type 1 Diabetes (Study TN-10)[a]

	Tzield N=44	**Placebo N=32**
Glucose, mg/dL[b]		
Median (min, max)	165 (115, 207)	154 (103, 200)
HbA1c, %		
Median (min, max)	5.2 (4.6, 6.1)	5.3 (4.3, 5.6)
HLA-DR4		
agMissing	5%	0
Absent	34%	34%
Present	61%	66%
HLA-DR3		
Missing	5%	0
Absent	48%	53%
Present	48%	47%
HLA-DR3/DR4		
Both DR3 and DR4	25%	22%
DR3 only	23%	25%
DR4 only	36%	44%
Missing	5%	0
Neither DR3 nor DR4	11%	9%
Autoantibodies Positive (N)		
1	2%	0
2	27%	22%
3	25%	16%
4	27%	44%
5	18%	19%
Autoantibody Type Positive		
GAD65	91%	88%
IAA	43%	34%
IA-2A	59%	75%

ICA	66%	88%
ZnT8	73%	75%

[a] Intent to treat (ITT) population.
[b] The glucose data are area under the time-concentration curve (AUC) values from the oral glucose tolerance test.
HbA1c: hemoglobin A1c; SD: standard deviation; HLA: human leukocyte antigen; GAD65: Glutamic acid decarboxylase 65 (GAD) autoantibodies; IAA: Insulin autoantibody, IA-2A: Insulinoma-associated antigen 2 autoantibody; ZnT8A: Zinc transporter 8 autoantibody; ICA: Islet cell autoantibody.

Efficacy Results

In Study TN-10, 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).

Study TN-10 was not designed to assess whether there were differences in the effectiveness between subgroups based on demographic characteristics or baseline disease characteristics.

Summary of Evidence

Based on the results of the clinical trial provided to the U.S. Food and Drug Administration for approval, Teplizumab-mzwv (Tzield®) may be considered medically necessary for adult and pediatric patients ≥ 8 years of age with confirmed stage 2 type 1 diabetes who meet all criteria outlined in the coverage section of this medical policy. Teplizumab-mzwv (Tzield®) is considered experimental, investigational, and/or unproven for all other indications or when used as a repeat course of treatment (beyond the initial 14 doses).

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 4.

Table 4. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04270942	At-Risk for Type 1 Diabetes Extension Study	30	Aug 2024
NCT04598893	Recent-Onset Type 1 Diabetes Extension Study Evaluating the Long-Term Safety of Teplizumab	200	June 2026

NCT05757713	Teplizumab in Pediatric Stage 2 Type 1 Diabetes (PETITE-T1D)	20	Oct 2026
Unpublished			
NCT03875729	Recent-Onset Type 1 Diabetes Trial Evaluating Efficacy and Safety of Teplizumab (PROTECT)	300	May 2023

NCT: national clinical trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J9381, [Deleted 7/2023: C9149]

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

References

1. American Diabetes Association. Classification and Diagnosis of Diabetes: Standards of Medical Care – Jan 2023. Diabetes Care 2023; 46(Suppl.1):S19-S40. Available at <https://care.diabetesjournals.org> (accessed February 22, 2024).
2. Greenbaum C, Lord S, Speake C. Type 1 diabetes mellitus: Disease prediction and screening. In UpToDate, Hirsch IB, Wolfsdorf JI (Eds), UpToDate, Waltham, MA. Available at <https://www.uptodate.com> (accessed February 22, 2024).
3. Hirsch IB. Pathogenesis of type 1 diabetes mellitus. In UpToDate, Nathan DM (Ed), UpToDate, Waltham, MA. Available at <https://www.uptodate.com> (accessed February 22, 2024).
4. Elsevier: Clinical Overview: Diabetes Mellitus Type 1 in Children. Updated Oct 16, 2023. (accessed February 22, 2024).
5. FDA – Highlights of Prescribing Information – Tzield™ (teplizumab-mzwv). Revised 11/2022. Available at <https://www.accessdata.fda.gov> (accessed February 22, 2024).

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <http://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
04/01/2024	Document updated with literature review. Coverage unchanged. No new references added; others updated/removed.
09/15/2023	Reviewed. No changes.
04/01/2023	New medical document. Teplizumab-mzwv (Tzield™) may be considered medically necessary for adult and pediatric patients ≥ 8 years of age with confirmed stage 2 type 1 diabetes who meet all criteria outlined in the coverage section of this medical policy. Teplizumab-mzwv (Tzield™) is considered experimental, investigational, and/or unproven for all other indications or when used as a repeat course of treatment (beyond the initial 14 doses).