MEDICAL COVERAGE POLICY	
SERVICE: Teplizumab-mzwv (Tzield™)	
Policy Number:	**303**
Effective Date:	**08/01/2023**
Last Review:	**06/28/2023**
Next Review Date:	**06/28/2024**

Important note:
Unless otherwise indicated, this policy will apply to all lines of business.
Even though this policy may indicate that a particular service or supply may be considered medically necessary and thus covered, this conclusion is not based upon the terms of your particular benefit plan. Each benefit plan contains its own specific provisions for coverage and exclusions. Not all benefits that are determined to be medically necessary will be covered benefits under the terms of your benefit plan. You need to consult the Evidence of Coverage (EOC) or Summary Plan Description (SPD) to determine if there are any exclusions or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and your plan of benefits, the provisions of your benefits plan will govern. However, applicable state mandates will take precedence with respect to fully insured plans and self-funded non-ERISA (e.g., government, school boards, church) plans. Unless otherwise specifically excluded, Federal mandates will apply to all plans. With respect to Medicare-linked plan members, this policy will apply unless there are Medicare policies that provide differing coverage rules, in which case Medicare coverage rules supersede guidelines in this policy. Medicare-linked plan policies will only apply to benefits paid for under Medicare rules, and not to any other health benefit plan benefits. CMS's Coverage Issues Manual can be found on the CMS website. Similarly, for Medicaid-linked plans, the Texas Medicaid Provider Procedures Manual (TMPPM) supersedes coverage guidelines in this policy where applicable.

SERVICE: Medications Covered Under Medical Policy

PRIOR AUTHORIZATION: Required

POLICY:

For Medicaid plans, please confirm coverage as outlined in the Texas Medicaid TMPPM. Texas Mandate HB1584 is applicable for Medicaid plans.

For Medicare plans, please refer to appropriate Medicare coverage policies at CMS.gov (e.g. Local Coverage Determination (LCD) documents and Articles, National Coverage Determination (NCD) documents, etc.) and apply Appendix A from this policy if applicable. If there is no applicable Medicare coverage policy or more specific medical policy, then use this policy.

Baylor Scott & White Health Plan (BSWHP) may consider teplizumab (Tzield™) medically necessary to delay the onset of Stage 3 type 1 diabetes (T1D) when ALL of the following criteria are met:

1) The member has a diagnosis of Stage 2 T1D; **AND**
2) The medication is prescribed by or in consultation with an endocrinologist; **AND**
3) The member is ≥ 8 years old; **AND**
4) The member has both of the following:
   a) Documentation of the presence of at least two of the following pancreatic islet autoantibodies:
      i) Glutamic acid decarboxylase 65 (GAD65) autoantibody
      ii) Insulin autoantibody (IAA)
      iii) Insulinoma-associated antigen 2 autoantibody (IA-2A)
      iv) Zinc transporter 8 autoantibody (ZnT8A)
      v) Islet cell autoantibody (ICA)

      AND
   b) Documentation of dysglycemia without overt hyperglycemia conducted within 2 months of the request as demonstrated by at least ONE of the following results on an oral glucose tolerance test (OGTT) or alternative method if appropriate and OGTT is not available:
      i) Fasting blood glucose level of 110 to 125 mg/dL (6.1 to 6.9 mmol/L)

ii) 2-hour post-prandial glucose of 140 to 199 mg/dL (7.8 to 11.0 mmol/L)
iii) Postprandial glucose level at 30, 60, or 90 minutes > 200 mg/dL (11.1 mmol/L);
AND

5) The member does NOT have any of the following:
   a) Clinical diagnosis of T1D (i.e. Stage 3 T1D)
   b) Type 2 diabetes
   c) Lymphocyte count less than 1,000 lymphocytes/mcL
   d) Hemoglobin less than 10 g/dL
   e) Platelet count less than 150,000 platelets/mcL
   f) Absolute neutrophil count less than 1,500 neutrophils/mcL
   g) Elevated ALT or AST greater than 2 times the upper limit of normal (ULN) or bilirubin greater than 1.5 times ULN
   h) Laboratory or clinical evidence of acute infection with Epstein-Barr virus (EBV) or cytomegalovirus (CMV)
   i) Active serious infection or chronic active infection other than localized skin infections

Approval will be for a one-time 14-day treatment course per lifetime.

BSWHP considers repeat administration of teplizumab experimental and investigational because the effectiveness of this strategy has not been established.

BSWHP considers teplizumab to be experimental and investigational for all other indications.

OVERVIEW:

Type 1 Diabetes (T1D) is a chronic, progressive autoimmune condition in which the pancreas does not produce enough insulin due to destruction of beta cells. According to the Centers for Disease Control and Prevention (CDC), about 5%–10% of people with diabetes have type 1, which usually develops in children, teenagers, and young adults, but could happen at any age. An estimated 1.6 million Americans are living with T1D (200,000 youth [<20 years of age] and 1.4 million adults [≥20 years of age]). Approximately 64,000 people are diagnosed with T1D each year, and 5 million people are expected to have T1D by 2040, including nearly 600,000 youth.

Patients who have a genetic susceptibility to developing T1D progress through stages before developing overt hyperglycemia requiring insulin treatment.

• Stage 1 is defined by the appearance of autoantibodies indicating the immune system has started attacking beta cells in the pancrease.

• Stage 2 involves asymptomatic dysglycemia.

• At Stage 3, significant autoimmune destruction of beta cells has occurred, so blood glucose is elevated and patients are symptomatic and require insulin treatment.

Eventually, all patients with T1D have to monitor blood sugar levels and are at risk of the same complications as patients with type 2 diabetes (T2D). Acute complications include diabetic ketoacidosis which can be potentially life-threatening. Long term damage includes cardiovascular disease, kidney damage, eye disease, and nerve damage.

The American Diabetes Association (ADA) recommends screening for autoantibodies in patients with first-degree relatives with T1D. The presence of multiple autoantibodies increases the probability for T1D; 70% of patients with T1D have 3 or 4 autoantibodies, while only 10% have a single autoantibody. The peak age of T1D diagnosis is around 13–14 years, but people can be diagnosed much younger or older. Currently, broad-population screening for T1D does not occur.

Interventions at Stage 1 or Stage 2 may delay the progression to Stage 3 T1D. While islet cell transplantation has been used, this treatment requires lifelong immunosuppression.

Teplizumab (Tzield) is the first FDA-approved pharmacological therapy for delaying the onset of clinical T1D, and was granted Breakthrough Therapy Designation by the FDA and PRIME designation by the European Medicines Agency (EMA). Teplizumab is an intravenously (IV) administered anti-CD3-directed antibody designed to bind to certain immune system cells and delay progression to Stage 3 T1D. Teplizumab is an Fc receptor nonbinding anti-CD3 monoclonal antibody that modifies CD8+ T lymphocytes, which are thought to be the important effector cells that kill insulin-producing beta cells in the pancreas.

In the Phase 2 multicenter TN-10 trial (NCT01030861), teplizumab delayed the onset of Stage 3 T1D by approximately 2 years compared to placebo. It was studied in patients 8 years of age and older who were at high risk of developing clinical diabetes. 76 patients were randomly assigned 1:1 to either teplizumab or placebo. A total of 20 (45%) of the 44 participants who received teplizumab and 23 (72%) of the 32 participants who received placebo had T1D diagnosed over a median follow-up of 51 months. With a median follow-up time of 51 months, therapy with teplizumab resulted in a statistically significant delay in development of Stage 3 T1D, hazard ratio (HR) 0.41 (95% confidence interval [CI]: 0.22 to 0.78; P = 0.0066). The most common adverse reactions (>10%) were lymphopenia, rash, leukopenia and headache

Teplizumab is administered once daily for 14 consecutive days, with no additional teplizumab treatment approved. If a planned infusion is missed, dosing is resumed by administering all remaining doses on consecutive days to complete the 14-day treatment course.

CODES:

Important note:

CODES: Due to the wide range of applicable diagnosis codes and potential changes to codes, an inclusive list may not be presented, but the following codes may apply. Inclusion of a code in this section does not guarantee that it will be reimbursed, and patient must meet the criteria set forth in the policy language.

CPT Codes:	96365 Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour 93413 Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug
CPT Not Covered:	
HCPCS code:	C9149 Injection, teplizumab-mzwv, 5 mcg J3590 unclassified biologics J9381 Injection, teplizumab-mzwv, 5 mcg

ICD10 codes:	E10.10 – E10.9 Type 1 diabetes mellitus
ICD10 Not covered:	

CMS:

POLICY HISTORY:

Status	Date	Action
New	06/28/2023	New policy

REFERENCES:

The following scientific references were utilized in the formulation of this medical policy. BSWHP will continue to review clinical evidence related to this policy and may modify it at a later date based upon the evolution of the published clinical evidence. Should additional scientific studies become available and they are not included in the list, please forward the reference(s) to BSWHP so the information can be reviewed by the Medical Coverage Policy Committee (MCPC) and the Quality Improvement Committee (QIC) to determine if a modification of the policy is in order.

1) Centers for Disease Control and Prevention (CDC). What is type 1 diabetes? Last reviewed March 11, 2022. Accessed November 30, 2022. https://www.cdc.gov/diabetes/basics/what-is-type-1-diabetes.html
2) Crossen S, et al. Changing costs of type 1 diabetes care among US children and adolescents. Pediatr Diabetes. 2020;21(4):644-648. doi:10.1111/pedi.12996
3) Ghalwash M, et al. Two-age islet-autoantibody screening for childhood type 1 diabetes: a prospective cohort study. Lancet Diabetes Endocrinol. 2022;10(8):589–596. doi:10.1016/S2213-8587(22)00141-3
4) Hagopian W, Ferry RJ Jr, Sherry N, 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. doi:10.2337/db13-0236
5) Herold KC, Gitelman SE, Ehlers MR, 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. 2013a;62(11):3766-3774. doi:10.2337/db13-0345
6) Herold KC, Gitelman SE, Willi SM, et al. Teplizumab treatment may improve C-peptide responses in participants with type 1 diabetes after the new-onset period: a randomised controlled trial. Diabetologia. 2013b;56(2):391-400. doi:10.1007/s00125-012-2753-4
7) Herold KC, et al. An anti-CD3 antibody, teplizumab, in relatives at risk for type 1 diabetes [published correction appears in N Engl J Med. 2020 Feb 6;382(6):586]. N Engl J Med. 2019;381(7):603–613. doi:10.1056/NEJMoa1902226
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9) Juvenile Diabetes Research Foundation (JDRF). Type 1 diabetes facts. Accessed November 29, 2022. https://www.jdrf.org/t1d-resources/about/facts/
10) Mital, S, et al. Cost effectiveness of teplizumab for prevention of type 1 diabetes among different target patient groups. PharmacoEconomics. 2020;38(12):1359–1372. doi:10.1007/s40273-020-00962-y
11) Perdigoto AL, Preston-Hurlburt P, Clark P, et al. Treatment of type 1 diabetes with teplizumab: clinical and immunological follow-up after 7 years from diagnosis. Diabetologia. 2019;62(4):655-664. doi:10.1007/s00125-018-4786-9
12) Regnell SE, Lernmark Å. Early prediction of autoimmune (type 1) diabetes. Diabetologia. 2017;60(8):1370-1381. doi:10.1007/s00125-017-4308-1

13) Sherry N, Hagopian W, Ludvigsson J, et al. Teplizumab for treatment of type 1 diabetes (Protégé study): 1-year results from a randomised, placebo- controlled trial. Lancet. 2011;378(9790):487-497. doi:10.1016/S0140-6736(11)60931-8
14) Sims EK, et al. Teplizumab improves and stabilizes beta cell function in antibody-positive high-risk individuals. Sci Transl Med. 2021;13(583):eabc8980. doi:10.1126/scitranslmed.abc8980
15) Sims EK, Cuthbertson D, Herold KC, Sosenko JM. The deterrence of rapid metabolic decline within 3 months after teplizumab treatment in individuals at high risk for type 1 diabetes. Diabetes. 2021b;70(12):2922-2931. doi:10.2337/db21-0519