Teplizumab-mzwv (TZIELD)
National Drug Monograph
March 2023
VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- Type 1 diabetes (T1D) is an autoimmune disease characterized by t-cell mediated destruction of beta cells within the pancreas that produce insulin.

- There are 3 stages of T1D. Stage 1 diabetes is defined as the presence of two or more autoantibodies with normal glucose tolerance. Stage 2 is defined as abnormal glucose tolerance in the presence of 2 or more autoantibodies. Stage 3 is the clinical diagnosis of T1D, which is often but not always accompanied by symptoms.

- Teplizumab-mzwv is a CD3-directed antibody that binds to CD3 (a cell surface antigen present on T lymphocytes) and delays the onset of T1D in those with Stage 2 T1D. The mechanism may involve partial agonistic signaling and deactivation of pancreatic beta cell autoreactive T lymphocytes. Teplizumab-mzwv leads to an increase in the proportion of regulatory T cells and of exhausted CD8+ T cells in peripheral blood.

Indication(s) Under Review in This Document

- Indicated to delay the onset of Stage 3 type 1 diabetes (T1D) in adults and pediatric patients aged 8 years and older with Stage 2 T1D.

Dosage Form(s) Under Review

- Injection: 2 mg per 2 mL (1 mg/mL) single-dose vial
- Administer by intravenous infusion (over a minimum of 30 minutes) once daily for 14 days as follows: 65 mcg/m2 (day 1); 125 mcg/m2 (day 2); 250 mcg/m2 (day 3); 500 mcg/m2 (day 4); 1,030 mcg/m2 (days 5-14)
- Premedicate prior to infusion of teplizumab for the first 5 days of dosing with: (1) a nonsteroidal anti-inflammatory drug or acetaminophen, (2) an antihistamine, and/or antiemetic. Additional doses may be given if needed.

Clinical Evidence Summary

Efficacy Considerations

Study TN-10 is a phase 2 randomized, double-blind, placebo-controlled study comparing teplizumab (n=44) versus placebo (n=32) in patients aged 8-45 years with Stage 2 T1D. Patients received study treatment once daily by intravenous infusion for 14 days. Teplizumab was dosed as follows: Day 0: 51 mcg/m2; Day 1: 103 mcg/m2; Day 2: 207 mcg/m2; Day 3: 413 mcg/m2; Days 4-13: 826 mcg/m2. Ibuprofen and antihistamine were administered prophylactically prior to teplizumab/placebo infusion on the first 5 days of treatment. Further dosing of Ibuprofen, antihistamines, and/or acetaminophen was used as needed for fever, malaise, headache, arthralgia, or rash.

The primary outcome was the time from randomization to clinical diagnosis of T1D.

The study population was identified through the TrialNet Natural History Study. Initial testing for autoantibodies, type 1 diabetes associated major histocompatibility complex molecules (HLA-DR3 and HLA-DR4), and Oral Glucose Tolerance Test (OGTT) was done as part of Natural History screening.

Key inclusion criteria for teplizumab trial:

- Has relative with T1DM. If relative is a parent, sibling, or offspring, the study participant must be 8-45 years of age. If relative is a second or third degree relative the study participant must be 8-20 years of age.
- Dysglycemia during oral glucose tolerance test (OGTT) on 2 occasions within 52 days prior to enrollment with at least one of the following: Fasting plasma glucose ≥ 110 mg/dL to < 126 mg/dl or 2-hour plasma glucose ≥ 140 mg/dL to < 200 mg/dl or 30, 60, or 90-minute value on OGTT ≥200mg/dl
- At least 2 of the following pancreatic islet autoantibodies detected in 2 samples within 6 months prior to randomization: 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).

Key exclusion criteria:

- Type 1 or type 2 diabetes
- Abnormal lab values (i.e., lymphopenia, neutropenia, thrombocytopenia, anemia, liver function tests, total bilirubin, etc.)
- Clinically important medical history. See protocol in the supplementary material of original article for complete list of exclusion criteria.

In the overall population, 55% were male, median age 14 years, 72% were less than 18 years old, 71% positive for 3 or more autoantibodies, HLA-DR3 absent 51%, HLA-DR4 present 64%. Relative with T1D: 58% sibling, 16% offspring, 12% parent, 7% sibling + another first-degree relative, 7% second-degree relative. Anti-GAD65 positive 89%, micro insulin positive 43%, anti-1A2 positive 67%, islet cell-autoantibody positive 75%, Anti-ZnT8 positive 74%

The median follow-up duration was 745 days (range 74 to 2683). Duration of follow-up was more than 3 years in 57 patients (75%). Efficacy data are summarized in Table 1.

Table 1: Efficacy results from Study TN-10

	Teplizumab (n=44)	Placebo (n=32)	Subgroup analysis
Diagnosis of T1D n(%)	20 (45%)	23 (72%)	More robust response to teplizumab was associated with: **-HLA-DR4 present:** HR=0.20 [95%CI 0.09, 0.45] **-HLA-DR3 absent:** HR=0.18 [95%CI 0.07, 0.45] **-Anti-ZnT8 autoantibody negative:** HR=0.07 [95%CI 0.02, 0.26] **-C-peptide response to OGTT below 1.75nmol/L:** HR=0.19 [95%CI 0.08, 0.47]
HR for diagnosis of T1D	0.41 (CI 0.22 to 0.78; p=0.006)		
Median time to diagnosis of T1D (mos.)	48.4	24.4	
Annualized rate of diagnosis of T1D (%/yr)	14.9%	35.9%	

Abbreviations: HR=hazard ratio; OGGTT=oral glucose tolerance test; T1D=type 1 diabetes

In an extended follow-up of Study TN-10 for a median of 923 days (range 74 to 3,119), 22/44 (50%) and 25/32 (75%) of the teplizumab and placebo treated groups respectively were diagnosed with T1D. The median times to diagnosis of T1D were 59.6 months (teplizumab) and 27.1 months (placebo); hazard ratio, 0.457; P = 0.01. Among 13 patients followed beyond 60 months, 8 in the teplizumab group and 2 in the placebo group were not diagnosed with T1D.

Safety Considerations

- **Boxed warnings:** None
- **Contraindications:** None
- **Other warnings / precautions**:
  - **Cytokine Release Syndrome (CRS**)
    CRS was reported in 2% of teplizumab treated patients compared to 0% of placebo-treated patients. Most cases were mild or moderate and none required intensive care. Symptoms included fever, nausea, fatigue, headache, myalgia, arthralgia, elevated ALT/AST/total bilirubin and typically occurred during the first 5 days of treatment. Premedicate prior to teplizumab infusion for the first 5 days as described under the Dosage Form section. Monitor liver enzymes, discontinue in those that develop elevated ALT or AST more than 5 times the upper limit of normal. Treat symptoms of CRS with antipyretics, antihistamines and/or antiemetics. If severe CRS develops, consider temporarily pausing dosing for 1-2 days (and administer the remaining doses to complete the full 14-day course on consecutive days) or discontinuing treatment.
  - **Serious Infections**
    Serious infections (cellulitis, gastroenteritis, pneumonia, wound infection) were reported in 9% of teplizumab-treated patients compared to 0% of placebo-treated patients any time during or after the first dose of study treatment. Use of teplizumab is not recommended in patients with active serious infection or chronic infection. Monitor for signs and symptoms of infection during and after teplizumab treatment. If a serious infection develops, discontinue treatment.
  - **Lymphopenia**
    The average lymphocyte count nadir occurred at Day 5 of treatment (total decrease was 72.3%), with recovery and return to baseline by Week 6. Monitor white blood cell counts during the treatment period. If prolonged severe lymphopenia (<500 cells/µL lasting 1 week or longer) develops, discontinue teplizumab
  - **Hypersensitivity Reactions**
    If severe hypersensitivity reactions occur, discontinue teplizumab and treat promptly.
  - **Vaccinations**
    Administer all age-appropriate vaccinations prior to starting teplizumab. Administer live-attenuated (live) vaccines at least 8 weeks prior to treatment. Administer inactivated (killed) vaccines or mRNA vaccines at least 2 weeks prior to treatment.

- **Adverse reactions**
  - **Common:** Most common adverse reactions (>10%) were lymphopenia, rash, leukopenia and headache
  - **Serious Adverse Events:**
    - Infections (9% vs 0%) all infections occurred more than 2 weeks after completion of teplizumab treatment course and were not temporally related to lymphonpenia or temporary immunosuppression with teplizumab
    - Serum sickness (n=1) 5 days after the completion of teplizumab treatment course
    - Isolated events and unlikely related to teplizumab: dizziness, concussion, ankle fracture, musculoskeletal chest pain and pelvic-ureteric obstruction
  - **Deaths:** None
  - **Discontinuations:** 3 (teplizumab), 4 (placebo)

Table 2: Common Adverse Reactions in Study TN-10 in at least 2 Patients

	Teplizumab (n=44)	Placebo (n=32)
Lymphopenia (%)	73	6
Rash (%)	36	0
Leukopenia (%)	21	0
Headache (%)	11	6
Neutropenia (%)	5	3
Increased aminotransferase (%)	5	3
Nausea (%)	5	3
Diarrhea (%)	5	0
Nasopharyngitis (%)	5	0

Data from product package insert

Immunogenicity: approximately 57% of teplizumab-treated patients developed anti-teplizumab-mzwv antibodies, 46% of whom developed neutralizing antibodies. The effects on clinical outcomes are not fully known at this time. There was a slightly higher incidence of rash in teplizumab-treated patients who developed anti-teplizumab-mzwv antibodies (39%) compared to those who did not develop anti-teplizumab-mzwv antibodies (33%).

Additional Safety Data

Data pooled from 5 trials, 4 of which were conducted in non-approved indications in patients with new- or recent-onset T1D, provides additional safety information. Refer to the FDA clinical review of teplizumab for more safety information obtained during the clinical trials for non-approved indications.

Table 3: Pooled Safety Data from 5 trials

	Teplizumab (n=773)	Placebo/standard of care (n=245)
Lymphopenia	77%	9%
Leukopenia	82%	24%
Rash	48%	15%
Anemia	27%	21%
Increased aminotransferases	25%	11%
Decreased calcium	19%	13%
Decreased bicarbonate	15%	7%
Thrombocytopenia	13%	5%
ALT > 3xULN	5.1%	0.8%
Cytokine release syndrome	5%	0
Urticaria	1.9%	1.2%
Peripheral/generalized edema	1.6%	0
Angioedema	0.3%	0
Serious rash	0.3%	0
Anaphylaxis	n=1	0

Data from product package insert. Data for lymphopenia and leukopenia are from the FDA review

Other Considerations

- Teplizumab is available to VA pharmacies as a wholesale order from Cardinal Health Specialty
- Prior to initiating teplizumab, obtain a complete blood count and liver enzyme tests. Teplizumab is not recommended in patients with:
  - Lymphocyte count less than 1,000 lymphocytes/mcL
  - Hemoglobin less than 10 g/dL
  - Platelet count less than 150,000 platelets/mcL
  - Absolute neutrophil count less than 1,500 neutrophils/mcL

  - Elevated ALT or AST greater than 2 times the upper limit of normal (ULN) or bilirubin greater than 1.5 times ULN
  - Laboratory or clinical evidence of acute infection with Epstein-Barr virus (EBV) or cytomegalovirus (CMV)
  - Active serious infection or chronic active infection other than localized skin infections
- Females of reproductive potential should have a pregnancy test prior to treatment with teplizumab. Patients should not receive teplizumab during pregnancy and at least 30 days before a planned pregnancy. Patients who become pregnant while taking teplizumab are encouraged to report their pregnancy to the Provention Bio's Adverse Event reporting line at 1-844-778-2246.
- It is not known if teplizumab passes into breast milk and whether it can harm the baby. If breastfeeding, consider pumping and throwing away the breast milk during treatment with teplizumab and for 20 days after receiving teplizumab treatment.
- In Study TN-10, only one course of therapy was given. The effect of repeated courses is unknown.
- it is unknown whether this 2-year median delay in the diagnosis of T1D will make an impact on the preventing long-term complications of T1D.
- Earlier studies with teplizumab had been conducted in new- or recent-onset T1D (AbATE, Delay, Protégé, and Encore). Teplizumab is not FDA-approved for new- or recent-onset T1D

Other Therapeutic Options: None

Projected Place in Therapy

The projected place in therapy for teplizumab is to delay the onset of T1D in individuals with Stage 2 T1D in adults up to age 45 years, who have a relative with T1D, have ≥2 pancreatic islet cell autoantibodies, and dysglycemia on OGTT and do not have any of the laboratory findings outlined in the product package insert that would preclude use of teplizumab.

REFERENCES

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Prepared January 2023. Contact person: Deb Khachikian, PharmD, National PBM Clinical Pharmacy Program Manager, Formulary management, VA Pharmacy Benefits Management Services