TZIELD is a CD3-directed antibody 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 (1).

**INDICATIONS AND USAGE**

TZIELD is intended to delay the onset of Stage 3 type 1 diabetes in adults and pediatric patients aged 8 years and older with Stage 2 T1D.

**DOSE AND ADMINISTRATION**

- Confirm Stage 2 T1D by documenting at least two positive pancreatic islet autoantibodies in those who have dysglycemia without overt hyperglycemia using an oral glucose tolerance test (OGTT) or alternative method if appropriate and OGTT is not available (2.1).
- 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 (2.2).
- Must dilute TZIELD in 0.9% Sodium Chloride Injection, USP. See full prescribing information for detailed preparation and administration instructions (2.3, 2.4, 2.5).
- Premedicate with: (1) a nonsteroidal anti-inflammatory drug (NSAID) or acetaminophen, (2) an antihistamine, and/or (3) an antiemetic before each TZIELD dose for at least the first 5 days of the 14-day treatment course (2.3).
- Administer TZIELD by intravenous infusion (over a minimum of 30 minutes) once daily for 14 days. See full prescribing information for the dosing schedule (2.4).

**DOSAGE FORMS AND STRENGTHS**

- Injection: 2 mg per 2 mL (1 mg/mL) single-dose vial (3).
- None. (4).

**CONTRAINDICATIONS**

- Cytokine Release Syndrome (CRS): Premedicate, monitor liver enzymes, discontinue in those that develop elevated ALT or AST more than 5 times the upper limit of normal, and, if severe CRS develops consider temporarily pausing dosing (5.1).
- Serious Infections: Use of TZIELD is not recommended in patients with active serious infection or chronic infection. Monitor for signs and symptoms of infection during and after TZIELD treatment. If a serious infection develops, discontinue TZIELD (5.2).
- Hypersensitivity Reactions: If severe hypersensitivity reactions occur, discontinue TZIELD and treat promptly (5.4).
- Vaccinations: Administer all age-appropriate vaccinations prior to starting TZIELD. See recommendations regarding live-attenuated, inactivated, and mRNA vaccines (2.2, 5.5).

**ADVERSE REACTIONS**

Most common adverse reactions (>10%) were lymphopenia, rash, leukopenia and headache (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Provention Bio at 1-800-633-1610 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

**USE IN SPECIFIC POPULATIONS**

- Pregnancy: May cause fetal harm (8.1).
- Lactation: A lactating woman may consider pumping and discarding breast milk during and for 20 days after TZIELD administration (8.2).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 12/2023
**6 ADVERSE REACTIONS**

The following serious adverse reactions are described elsewhere in the prescribing information:

- Cytokine Release Syndrome [see Warnings and Precautions (5.1)]
- Serious Infections [see Warnings and Precautions (5.2)]
- Lymphopenia (see Warnings and Precautions (5.3))
- Hypersensitivity Reactions [see Warnings and Precautions (5.4)]

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reactions observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

**Placebo-Controlled Study in Patients with Stage 2 Type 1 Diabetes**

The data in Table 1 are derived from the placebo-controlled study (Study TN-10) in patients ages 8 years and older with Stage 2 type 1 diabetes [T1D] [see Clinical Studies (14)]. These data reflect exposure of 44 patients of whom 93% completed the full 14-day treatment course.

**Pool of Five Controlled Clinical Studies in Stage 2 Type 1 Diabetes and in an Unapproved Population**

Adverse reactions in TZIELD-treated patients were also evaluated in a larger pool of adult and pediatric patients who participated in five controlled clinical studies (including Study TN-10 described above):

- One study in patients with Stage 2 T1D (Study TN-10) [see Clinical Studies (14)].
- Three placebo-controlled studies in an unapproved population.
- One open-label standard-of-care controlled study of TZIELD in an unapproved population.

In this pool:

- 737 patients received TZIELD (44 patients with Stage 2 T1D and 729 patients from an unapproved population), and
- 245 patients received either placebo or standard of care control (32 patients with Stage 2 T1D and 213 patients from an unapproved population).

In these studies, 436 patients received a 14-day course of TZIELD with a total drug exposure that was comparable to the total drug exposure achieved with the recommended dosage [see Dosage and Administration (2.4)]. 168 patients received a 14-day course of TZIELD with a lower total TZIELD drug exposure, and 169 patients received a 6-day course of TZIELD with a lower total TZIELD drug exposure. The mean age of TZIELD-treated patients was 17.6 years (median 15 years), 82% were <18 years old (40% age 12 to 17; 21% age 8 to 11), and 64% were male. The population was 72% White, 28% Asian, 1% Black or African American, 1% were multiple or unknown race, and <1% American Indian or Alaska Native; 5% were Hispanic or Latino ethnicity.

**Common Adverse Reactions**

Table 1 presents common (≥5%) adverse reactions that occurred during treatment and through 28 days after the last study drug administration in Study TN-10. Adverse reactions observed in pediatric patients 8 years and older who received TZIELD were consistent with those reported in adult patients in this study.

### Table 1. Common Adverse Reactions in Adult and Pediatric Patients Aged 8 Years and Older with Stage 2 Type 1 Diabetes (Study TN-10)\(^1\)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo N=32</th>
<th>TZIELD N=44</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphopenia</td>
<td>6%</td>
<td>73%</td>
</tr>
<tr>
<td>Rash*</td>
<td>0%</td>
<td>36%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>0%</td>
<td>21%</td>
</tr>
<tr>
<td>Headache</td>
<td>6%</td>
<td>11%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>Increased alamine aminotransferase</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>Nausea</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0%</td>
<td>5%</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>0%</td>
<td>5%</td>
</tr>
</tbody>
</table>

*That occurred during treatment and through 28 days after the last study drug administration.

†Composite of rash-related terms including rash erythematous, rash macular, rash papular, rash maculo-papular, rash pruritic.

**Cytokine Release Syndrome (CRS)**

In Study TN-10, CRS was reported in 2% of TZIELD-treated patients compared to 0% of placebo-treated patients.

Of the 436 TZIELD-treated patients that developed CRS (5% of all TZIELD-treated patients) in the pool of 5 clinical trials, 13% of the CRS cases were serious adverse reactions [see Warnings and Precautions (5.1)]. Liver transaminase elevations were observed in 56% of TZIELD-treated patients who experienced CRS; 64% were up to 2.5 times ULN, 32% were up to 5 times ULN, and 4.5% were 5-10 times ULN.

**Serious Infections**

In Study TN-10, serious infections (cellulitis, gastroenteritis, pneumonia, wound infection) were reported in 9% (4/44) of TZIELD-treated patients compared to 0% (0/32) of placebo-treated patients any time during or after the first dose of study treatment.

**Pneumonia**

**Hypersensitivity Reactions**

Hypersensitivity reactions were reported with TZIELD in Study TN-10. Serum sickness was observed in 2% (1/44) of TZIELD-treated patients compared to 0% (0/32) of placebo-treated patients. The patient who developed serum sickness had a prior history...
of positive anti-nuclear antibody and presented with arthralgias and elevated c-reactive protein and low C3 complement five days after completing their course of TZIELD, illness resolved in 2.5 months.

In the pool of 5 clinical trials of patients:
- Anaphylaxis (with hypoxia and bronchospasm) was observed in one TZIELD-treated patient who was hospitalized.
- Angioedema (periorbital and facial) was observed in 0.3% TZIELD-treated patients, compared to 0% in control-treated patients. Peripheral and generalized edema was reported in 1.6% of TZIELD-treated patients and 0% of control-treated patients.
- Rash was observed in 48% of TZIELD-treated patients compared to 15% in control-treated patients, with 33 excess cases of rash per 100 patients. The majority of rashes observed with TZIELD treatment were not serious and resolved without intervention; although 0.3% (2/773) of TZIELD-treated patients had a serious rash compared to 0% (0/245) of placebo-treated patients.
- Urticaria was reported in 1.9% of TZIELD-treated patients and in 1.2% of control-treated patients.

Immunogenicity: Anti-Drug Antibody-Associated Adverse Reactions

In Study TN-10, lymphopenia was reported in 73% of TZIELD-treated patients compared to 6% of placebo-treated patients. The average lymphocyte count nadir occurred at Day 5 of treatment, with recovery and return to baseline by Week 6 [see Warnings and Precautions (6.3)].

Neutropenia

In Study TN-10, neutropenia was observed in 7% of TZIELD-treated patients compared to 3% of placebo-treated patients.

Anemia and Thrombocytopenia

In the pool of 5 clinical trials of patients, anemia was reported in 27% of TZIELD-treated patients compared to 21% of placebo-treated patients, and thrombocytopenia was reported in 13% of TZIELD-treated patients compared to 5% of placebo-treated patients during the course of TZIELD treatment and the nadir in platelet count was within 2 to 4 weeks of treatment. In clinical trials, 1.8% of TZIELD-treated patients discontinued treatment due to hemoglobin less than 8.5 g/dL (or a decrease of more than 2 g/dL to a value less than 10 g/dL) and 1% discontinued TZIELD due to platelet count less than 30,000 platelets/mcL.

Liver Enzyme Elevations

Liver enzyme elevations were observed in TZIELD-treated patients, both in the context of CRS and in patients without CRS. In the pool of 5 clinical trials, elevated aminotransferases were reported in 25% of TZIELD-treated patients compared to 11% of placebo-treated patients during the 14-day treatment course. On laboratory analysis, 5.1% of TZIELD-treated patients experienced a peak ALT more than 3 times the ULN compared to 0.8% of control-treated patients. Most liver enzyme elevations were transient and resolved 1-2 weeks after treatment; 98% resolved by follow-up week 14.

Other Laboratory Abnormalities

In the pool of 5 clinical trials, other laboratory abnormalities including decreased bicarbonate (15% in TZIELD-treated patients, compared to 7% in placebo-treated patients) and decreased blood calcium (19% in TZIELD-treated patients, compared to 13% in placebo-treated patients) were noted.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available case reports from clinical trials with TZIELD are insufficient to identify a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. Although there are no data on teplizumab-mzwv and monoclonal antibodies can be active in the placenta, transplacental transfer of antibodies to the fetus has been reported. In a clinical study of women with type 1 diabetes and anti-GAD antibodies, no cases of congenital anomalies were reported in the offspring of dams administered the murine surrogate antibody at 20 mg/kg. The human relevance of this finding is unknown.

8.2 Lactation

Risk Summary

There is no data on the presence of teplizumab-mzwv in either human or animal milk, or the effects on the breastfed child, or the effects on milk production. Endogenous maternal IgG and monoclonal antibodies are transferred into human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to teplizumab-mzwv are unknown.

Although the developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for TZIELD and any potential adverse effects on the breastfed child from TZIELD or from the underlying maternal condition, a lactating woman should be advised not to breastfeed until 20 days after TZIELD administration to minimize drug exposure to a breastfed child.

8.4 Pediatric Use

The safety and effectiveness of TZIELD to delay the onset of Stage 3 type 1 diabetes have been established in pediatric patients 8 years of age and older. Stage 2 type 1 diabetes. Use of TZIELD for this indication is supported by evidence from an adequate and well-controlled study (Study TN-10) in adults and pediatric patients 8 years of age and older (including 29 pediatric patients). Adverse reactions observed in pediatric patients 8 years of age and older who received TZIELD were consistent with those reported in adult patients [see Adverse Reactions (6.1)].

The safety and effectiveness of TZIELD have not been established in pediatric patients younger than 8 years of age.

11 DESCRIPTION

11.1 Mechanism of Action

Teplizumab-mzwv binds to CD3 (a cell surface antigen present on T lymphocytes) and delays the onset of Stage 3 type 1 diabetes in adults and pediatric patients 8 years of age and older. The mechanism may involve partial agonistic interaction with T-cell activation pathways.

11.2 Pharmacokinetics

Clinical studies have shown that teplizumab-mzwv binds to CD3 molecules on the surface of CD4+ and CD8+ T lymphocytes, and delays the onset of Stage 3 type 1 diabetes. Use of TZIELD for this indication is supported by evidence from an adequate and well-controlled study (Study TN-10) in adults and pediatric patients 8 years of age and older. Use of TZIELD did not include patients 65 years of age and older.

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The safety and effectiveness of TZIELD have not been established in pediatric patients younger than 8 years of age.
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) (continued)

<table>
<thead>
<tr>
<th>Autoantibodies Positive (N)</th>
<th>TZIELD N=44</th>
<th>Placebo N=32</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 autoantibody</td>
<td>11%</td>
<td>9%</td>
</tr>
<tr>
<td>2 autoantibodies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GAD65</td>
<td>91%</td>
<td>88%</td>
</tr>
<tr>
<td>IAA</td>
<td>43%</td>
<td>34%</td>
</tr>
<tr>
<td>IA-2A</td>
<td>59%</td>
<td>75%</td>
</tr>
<tr>
<td>ZnT8</td>
<td>66%</td>
<td>88%</td>
</tr>
<tr>
<td>ZnT8A</td>
<td>73%</td>
<td>75%</td>
</tr>
</tbody>
</table>

Abbreviations: HbA1c=hemoglobin A1c, SD=standard deviation, HLA = human leukocyte antigen, GAD65=Glutamic acid decarboxylase 65 (GAD) autoantibodies, IA-2A=Insulinoma-associated antigen 2 autoantibody, ZnT8=Zinc transporter 8 autoantibody, ICA=islet cell autoantibody

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies have been performed to assess the carcinogenic potential of teplizumab-mzwv.

No studies have been performed to assess the mutagenic potential of teplizumab-mzwv.

As an antibody, teplizumab-mzwv is not expected to interact directly with DNA. Fertility and reproductive performance were unaffected in female and male mice that received a murine surrogate anti-mouse CD3 antibody administered by the subcutaneous route at doses up to 20 mg/kg.

14 CLINICAL STUDIES

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:
   - 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 [see Dosage and Administration (2.4)]. 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) (Table 2).

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)

<table>
<thead>
<tr>
<th>Autoantibody Type</th>
<th>Positive N=44</th>
<th>Positive N=32</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAD65</td>
<td>91%</td>
<td>88%</td>
</tr>
<tr>
<td>IAA</td>
<td>43%</td>
<td>34%</td>
</tr>
<tr>
<td>IA-2A</td>
<td>59%</td>
<td>75%</td>
</tr>
<tr>
<td>ZnT8</td>
<td>66%</td>
<td>88%</td>
</tr>
<tr>
<td>ZnT8A</td>
<td>73%</td>
<td>75%</td>
</tr>
</tbody>
</table>

Abbreviations: HbA1c=hemoglobin A1c, SD=standard deviation, HLA = human leukocyte antigen, GAD65=Glutamic acid decarboxylase 65 (GAD) autoantibodies, IA-2A=Insulinoma-associated antigen 2 autoantibody, ZnT8=Zinc transporter 8 autoantibody, ICA=islet cell autoantibody

14 CLINICAL STUDIES

14.1 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) (Figure 1).

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.

Figure 1: Kaplan-Meier Curve of Time to Diagnosis of Stage 3 Type 1 Diabetes in Adult and Pediatric Patients Aged 8 Years and Older with Stage 2 Type 1 Diabetes by Treatment Group (Study TN-10)

14 HOW SUPPLIED / STORAGE AND HANDLING

TZIELD (teplizumab-mzwv) injection is a clear and colorless solution (2 mg/2 mL (1 mg/mL)) supplied in a single-dose vial as follows:

- Carton Contents NDC 73650-316-14 (1 single dose vial)
- Placebo NDC 73650-316-01 (1 single dose vial)
- Placebo NDC 73650-316-10 (1 single dose vial)

Refrigerate TZIELD vials at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Store upright. Do not freeze or shake the vials. If not used immediately, store the diluted solution at room temperature [15°C to 30°C (59°F to 86°F)] and complete infusion within 4 hours of the start of preparation. Discard the diluted solution if not administered within 4 hours of preparation [see Dosage and Administration (2.5)].

17 PATIENT COUNSELING INFORMATION

Advises the patient to read the FDA-approved patient labeling (Medication Guide).

Cytokine Release Syndrome

Inform patients about the signs and symptoms of CRS [see Warnings and Precautions (5.1)].
What is TZIELD?
TZIELD is a prescription medicine used to delay the onset of Stage 3 type 1 diabetes, which is when your body can’t make enough insulin on its own and may require insulin injections.
TZIELD is for adults and children 8 years of age and older who have Stage 2 type 1 diabetes. This means that they have tested positive for 2 or more type 1 diabetes-related autoantibodies, have abnormal blood sugar levels and do not have type 2 diabetes. It is not known if TZIELD is safe and effective in children under 8 years of age.

Before or after receiving TZIELD, tell your healthcare provider about all your medical conditions, including if you:
- have any of the conditions or symptoms listed in the section “What is the most important information I should know about TZIELD?”
- have a serious infection or an infection that does not go away or that keeps coming back (chronic).
- have recently received or are scheduled to receive an immunization (vaccine). TZIELD may affect how well a vaccine works. Tell your healthcare provider that you are receiving treatment with TZIELD before receiving a vaccine.
- are pregnant or plan to become pregnant. TZIELD may harm your unborn baby. Do not receive TZIELD during pregnancy and at least 30 days before a planned pregnancy.
- If you become pregnant while taking TZIELD, you are encouraged to report your pregnancy to the Provention Bio’s Adverse Event reporting line at 1-800-633-1610.
- are breastfeeding or plan to breast feed. It is not known if TZIELD is safe and effective in breastfeeding women. Advise a lactating woman that she may interrupt breastfeeding and pump and discard breast milk during treatment and for 20 days after TZIELD administration to minimize drug exposure to a breastfed infant.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive TZIELD?
- TZIELD is given by a healthcare provider through a needle placed in a vein (intravenous infusion) in your arm.
- You will receive a TZIELD infusion one-time a day, every day, for 14 days. Each TZIELD infusion will last about 30 minutes.
- For the first 5 days of treatment, your healthcare provider will give you medicines by mouth before starting your TZIELD infusion. These medicines include ibuprofen, naproxen or other pain relievers such as acetaminophen, an antihistamine, and an anti-nausea medicine. These medicines may help reduce symptoms of CRS such as a fever, headache, muscle and joint pain, or nausea.
- If you miss a scheduled infusion, your healthcare provider will continue your treatment on the next scheduled day. You will not receive 2 infusions on the same day.

Tell your healthcare provider if you think something will stop you from completing treatment with TZIELD.

What are the possible side effects of TZIELD?
TZIELD may cause serious side effects including:
- See “What is the most important information I should know about TZIELD?”

The most common side effects of TZIELD include:
- rash
- leukopenia (decrease in white blood cell counts)
- headache

These are not all of the possible side effects of TZIELD. For more information, ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088. You may also report side effects to Provention Bio at 1-800-633-1610.
General information about the safe and effective use of TZIELD.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about TZIELD that is written for health professionals.

What are the ingredients in TZIELD?
Active ingredient: teplizumab-mzwv.
Inactive ingredients: dibasic sodium phosphate, monobasic sodium phosphate, polysorbate 80, sodium chloride, and water for injection.

Manufactured by:
Provention Bio, Inc.
Bridgewater, NJ 08807

U.S. License Number: 2170

TZIELD is a registered trademark of Provention Bio, Inc.

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For more information, call 1-800-633-1610 or go to www.tzield.com.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Issued: 12/2023

TEP-FPLR-SL-DEC23

Rx Only