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CAREPATHrx™
Specialty Pharmacy & Infusion Solutions

# GUIDELINES FOR OUTPATIENT INTRAVENOUS TEPLIZUMAB (TZIELD)

**Section:** Clinical Guidelines
**Compliance:** Infusion Pharmacy
**ACHC Standards:** N/A
**URAC Standards:** N/A
**TJC Standards**: N/A
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**Approved by:** Kathleen Patrick, President, 2/13/23

## I. BACKGROUND

Tzield (Teplizumab-mzwv) 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. The mechanism may involve partial agonistic signaling and deactivation of pancreatic beta cell autoreactive T lymphocytes. Teplizumab leads to an increase in the proportion of regulatory T cells and of exhausted CD8+ T cells in peripheral blood. The following outlines the procedures for servicing patients in need of outpatient intravenous (IV) teplizumab infusions.

## II. PATIENT ACCEPTANCE CRITERIA

A. All candidates for home care service must be evaluated by the clinician(s) and deemed appropriate to receive home care based upon the dispensing pharmacy's admission criteria.

B. The decision to administer a first dose in the home by a field nurse will be determined on a case-by-case basis and reviewed by nursing and pharmacy management. The following criteria will be evaluated:
   1. Prescriber preference
   2. Allergy profile
   3. Pediatric patients
      a. The risk of cytokine release syndrome is higher during the first five days of treatment, based on clinical trials. It is recommended to initiate treatment in a controlled setting. Should home administration be necessary to initiate treatment, field nursing with Pediatric Advanced Life Support (PALS) certification is encouraged. Nurses should demonstrate previous pediatric experience.
   4. Other relevant social and/or medical history

C. Prior to initiation of therapy, the following should be documented:
   1. Confirmation of Stage 2 TID as evidenced by at least 2 positive pancreatic islet cell autoantibodies.
   2. Dysglycemia without over hyperglycemia using an oral glucose tolerance test (or alternative test)
   3. Completion of complete blood count, liver enzyme tests; Epstein-Barr Virus (EBV) or cytomegalovirus (CMV) testing if clinically appropriate
   4. Completion of age-appropriate vaccinations. Vaccination during treatment is not

recommended.
    a. Live-attenuated vaccines completed at least 8 weeks prior to OR 52 weeks after treatment.
    b. Inactivated or mRNA vaccines completed at least 2 weeks prior to OR 6 weeks after treatment.
5. Physician orders for teplizumab must include:
    a. Patient BSA, height, and weight
    b. Drug and dose
    c. Route of administration
    d. Frequency of administration
    e. Emergency medications
    f. Premedication directions, if applicable:
        i. Pre-medications required for days 1-5 of treatment:
            1) A nonsteroidal anti-inflammatory drug (NSAID) or acetaminophen
            2) An antihistamine, and/or
            3) Antiemetic.
        ii. Pre-medications beyond treatment day 5 is at the clinical judgement of the prescriber.
        iii. Pre-medications beyond Day 5 may be ordered at the provider's discretion based on patient response.
        iv. Oral or over-the-counter pre-medications may be obtained separately by the patient/caregiver.
    g. Line care protocol
    h. Routine lab monitoring, if applicable

6. Dispensing pharmacy treatment protocol for anaphylaxis will be instituted for adult patients unless a more comprehensive patient-specific orders are provided by physician. See policy NUR012 (Appendix A). Patient-specific orders are required for patients less than 18 years of age in the absence of an institutional pediatric protocol.

## III. PHARMACOLOGY OVERVIEW

**Refer to manufacturer's full Prescribing Information for most up to date information.**

A. Indications
    1. 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.

B. Dosage and Frequency
    1. Administer once daily for 14 days as follows:

| | |
|---|---|
| **Day 1** | 65mcg/$m^2$ |
| **Day 2** | 125mcg/$m^2$ |
| **Day 3** | 250mcg/$m^2$ |
| **Day 4** | 500mcg/$m^2$ |
| **Day 5 through day 14** | 1030mcg/$m^2$ |

2. BSA should be calculated using Mosteller formula based on patient height and actual body weight. Extremes of weight or BSA were not evaluated in clinical trials, body mass index of study participants ranged from 17.3 to 25.4kg/$m^{2.}$

C. Contraindications: None

D. Warnings and Precautions
   1. Cytokine Release Syndrome (CRS): In clinical trials, CRS was reported in 5% of teplizumab patients compared to 0.8% of control-treated patients during the treatment period and through 28 days after the last study drug administration. CRS manifestations in teplizumab patients included fever, nausea, fatigue, headache, myalgia, arthralgia, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), and increased total bilirubin. These manifestations typically occurred during the first 5 days of treatment. Mitigation of CRS may include:
      a. Premedication and/or symptomatic treatment with antipyretics, antihistamines, and/or antiemetics. If severe CRS develops, consider pausing dosing for 1-2 days or discontinuation of treatment.
      b. Monitoring of liver functions testing during treatment. Discontinue therapy in patients who develop AST or ALT > 5 times the upper limit of normal (ULN) or bilirubin > 3 times the upper limit of normal.
   2. Serious Infections: Bacterial and viral infections have occurred in teplizumab patients. In clinical trials, teplizumab patients had a higher rate of serious infections (3.5%) than control-treated patients (2%), including gastroenteritis, cellulitis, pneumonia, abscess, sepsis. Use is not recommended in patients with active serious infection or chronic infection other than localized skin infections. Monitor patients for signs and symptoms of infection during and after treatment. If serious infection develops, treat appropriately, and discontinue teplizumab.
   3. Lymphopenia: In clinical trials, 78% of teplizumab patients developed lymphopenia compared to 11% of control-treated patients. For most teplizumab patients who experienced lymphopenia, lymphocyte levels began to recover after the fifth day of treatment and returned to pre-treatment values within two weeks after treatment completion and without dose interruption. Severe lymphopenia (< 500 cells/mcL) lasting 1 week or longer occurred in 0.9% of teplizumab patients and 0.5% of patients permanently discontinued treatment because of lymphopenia. Monitor white blood cell counts during the treatment period. If prolonged severe lymphopenia develops, discontinue teplizumab.
   4. Hypersensitivity reactions: Acute hypersensitivity reactions including serum sickness and bronchospasm (2% compared to 0% of placebo-treated patients), angioedema (0.3% compared to 0% in control-treated patients), urticarial (1.9% of patients compared to 1.2% of control-treated patients), and rash (48% compared to 15% in control-treated patients). Most cases were not serious and resolved without intervention. If severe hypersensitivity reactions occur, discontinue teplizumab and treat promptly.
   5. Vaccinations: The safety of immunization with live-attenuated vaccines in teplizumab patients has not been studied. Additionally, teplizumab may interfere with the immune response to vaccination and decrease vaccine efficacy. Ensure age-appropriate vaccinations are up to date prior to starting treatment. Refer to *Patient Acceptance Criteria* above for timing of inactivated and live vaccines.

E. Pharmacokinetics
   1. Volume of distribution: 2.27 L
   2. Elimination half-life: 4.5 days

F. Adverse Reactions:

1. (>10%) lymphopenia, rash, leukopenia, headache
2. (>5%) neutropenia, increased ALT, nausea, diarrhea, nasopharyngitis
3. Immunogenicity: In clinical trials, approximately 57% of teplizumab patients developed anti-teplizumab-mzwv antibodies, 46% of whom developed neutralizing antibodies. There is insufficient information to characterize the effects of anti-drug antibodies (ADA) on pharmacokinetics, pharmacodynamics, or effectiveness of teplizumab. There was a higher incidence of rash in patients who developed anti-teplizumab-mzwv antibodies compared to those who did not develop anti-teplizumab-mzwv antibodies.

G. Pregnancy: Available case reports from clinical trials 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, monoclonal antibodies can be actively transported across the placenta, and teplizumab may cause immunosuppression in the utero-exposed infant. To minimize exposure to a fetus, avoid use of teplizumab during pregnancy and at least 30 days (6 half-lives) prior to planned pregnancy. Report pregnancies to Provention Bio, Inc.'s Adverse Event reporting line at 1-844-778-2246.

H. Lactation: Advise a lactating woman that she may interrupt breastfeeding and pump and discard breast milk during treatment and for 20 days after teplizumab administration to minimize drug exposure to a breastfed infant.

I. Drug Interactions: No documented drug interactions

## IV. ADMINISTRATIVE GUIDELINES

A. Administration: Teplizumab IV infusions should be given immediately after reconstitution and dilution. Begin infusion within 2 hours of preparation, with completion of infusion within 4 hours. If unable to complete infusion within 4 hours notify the pharmacy and discard the infusion solution.

B. Duration: Infuse once daily for 14 consecutive days. Do not administer more than one dose on the same day. If a planned infusion is missed, resume dosing by administering all remaining doses on consecutive days to complete the 14-day treatment course.

C. Dose Adjustment: No renal or hepatic dose adjustments are recommended. Use in patients with ALT/AST greater than 2 times the ULN or bilirubin greater than 1.5 times the ULN. Studies in patients 65 years of age or older were not conducted.

## V. NURSING PROCEDURE

A. Supplies may include but are not limited to:
   1. Alcohol Swabs
   2. Gloves
   3. Sharps container
   4. Syringes (3mL, 20mL) with needles (20 G x 1")
   5. Dressing change kit
   6. IV Pole
   7. IV Start Kit
   8. Peripheral IV catheter (ex. 22 Gauge x1" and 24 Gauge x ¾" for patients needing peripheral access)
   9. Tape

10. Extension set 8”
11. IV injection cap
12. Freedom 60 IV Precision Tubing
13. Freedom 60 pump

B. Prescription Items
    1. Teplizumab vial(s)
    2. Glass vial of 18mL of sodium chloride 0.9% for drug dilution
    3. 25mL NSS in a 50mL syringe for Freedom pump

C. How Supplied: Teplizumab injection is a clear and colorless solution supplied in a single-dose vial (2mg/2mL (1mg/1mL)).

D. Storage and Handling: Refrigerate teplizumab 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.

E. Compatibility: Dilute with 0.9% sodium chloride prior to use

F. Procedures:
    1. Explain the reasoning for visit and use of teplizumab infusion.
    2. Don gloves.
    3. Ensure patient administered oral premedications as ordered, if applicable.
    4. Establish venous access prior to preparation of drug.
    5. Counsel patient or caregiver on warnings, precautions, and potential side effects including but not limited to cytokine release syndrome, infections, hypersensitivity reactions, lymphopenia, rash, headache.
    6. Prepare Product:
        a. Inspect both 18ml vial of 0.9% NaCl and teplizumab vial visually before use (the supplied solution is clear and colorless). Do not use if particulate matter or coloration is seen.
        b. Remove 2ml (2mg) of teplizumab from the vial using aseptic technique. Slowly add to 18 mL vial of 0.9% Sodium Chloride. Mix gently by slowly inverting the vial. The resulting 20 mL diluted solution contains 100 mcg/mL of teplizumab.
        c. Using the provided 20 mL syringe with needle, withdraw the volume of diluted teplizumab solution required for that day’s calculated dose from the 100 mcg/mL solution.
        d. Slowly add contents of the syringe containing the teplizumab dose to the provided 50 mL syringe containing 25 mL 0.9% sodium chloride. Gently rotate the syringe to ensure that the solution mixes sufficiently. DO NOT SHAKE!
        e. Add Freedom 60 Precision Tubing to the 50 mL syringe and administer over at least 30 minutes.
    7. Infusion Rates: Infuse over at least 30 minutes.
    8. Monitor vitals periodically throughout the infusion and for at least 30 minutes after end of infusion per INS guidelines

## I. CLINICAL MONITORING

A. Prior to therapy:
    1. CBC, Liver function panel, and EBV/CMV testing

2. Ensure patient is up to date on vaccines and free of active infection.
3. Pregnancy status and effective contraception

B. During therapy:
    1. Monitor for signs and symptoms of Cytokine Release Syndrome.
        a. Use of pre-medications may mask symptoms.
        b. Observable CRS manifestations may include but are not limited to fever, nausea, fatigue, headache, myalgia, arthralgia.
            **i.** Myalgia, arthralgia, or malaise, when concurrent with fever, may be more suggestive of CRS etiology.
        c. Nurse will monitor vital signs during and immediately after infusion.
        d. Patient/caregiver may be instructed to monitor body temperature, pulse, blood pressure, and/or pulse oximetry, if able, beyond the nursing visit.
        e. Patients should seek immediate medical attention if signs/symptoms of CRS progress or persist; discontinuation or interruption in therapy may be required.
    2. Monitor for signs and symptoms of infection. Therapy is not recommended during active infection other than local skin infections.
    3. Signs and symptoms of a hypersensitivity reaction
    4. Signs or symptoms of lymphopenia. Monitor white blood cell counts during treatment.
    5. CBC and LFTs as prescribed by provider.

**Please refer to the package insert for the most up to date guidance on this medication.**

**REFERENCES:**

TZIELD [package insert]. Red Bank, NJ. Provention Bio, Inc. 2022.

## APPENDIX A: ANAPHYLAXIS KIT INTRUCTIONS

## Emergency Medication After Your Infusion

**Please call your pharmacy if you have any questions or concerns. In the event of an emergency, always call 911.**

**Your nurse will tell you when you need to use Emergency Medications.**
**The epinephrine dose will be noted on the Anaphylaxis Protocol included with your kit.**

Start with a clean work surface and clean hands.

**Open the supply bag labeled Anaphylaxis Kit Contents.**

**You will need:**

1. **Bag containing Pills** (2 Acetaminophen and 2 Diphenhydramine)
2. **Bag containing Alcohol Prep Pads**
3. **Bag labeled IM Epinephrine**

**All other contents will not be needed.**

**Open the IM Epinephrine Bag**

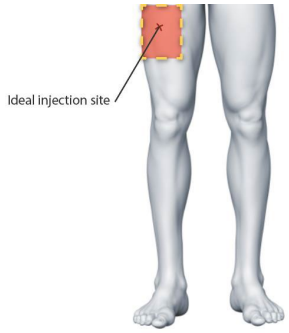
1. **Remove 1 of each item**
    a. 1 -syringe
    b. 1 – brown labeled filter needle (BD Filter Needle)- **for ampule use only**
    c. 1 – black labeled safety needle (Magellan Hypodermic Safety Needle 22G x 1")
    d. 1 ampule of epinephrine

**Prepare IM (intramuscular) injection of Epinephrine:**

1. **Attach the brown filtered needle to syringe**
    a. Be careful to not touch the tip of the syringe or the needle.
2. Using an **alcohol swab, wipe the neck of the epinephrine ampule.**
3. Holding the ampule upright, **swirl and flick the ampule until all fluid flows to the bottom chamber** (the top chamber should be empty).
4. Using a new alcohol wipe, grasp the neck of the ampule and with your other hand grasp the bottom chamber of the ampule. **Quickly snap the top of the ampule off, directing the snap way from you.**
5. **Place the tip of the brown filter needle inside the ampule**. Tilting the ampule, **withdraw dose of medication into the syringe** by gently pulling back on the plunger. Be careful to not pull the plunger out of the syringe.
6. Remove the needle from the ampule and h**old the syringe upright** with the needle pointing upward. **Gently tap the side of the syringe to bring any air to the top of the syringe.**
7. **Push the air out of the syringe by gently pushing on the plunger**.
8. Replace the cap on the brown filter needle. Discard remainder in ampule.

9. **Remove the brown filter needle and place the black safety needle onto the syringe.**

Give your IM Epinephrine injection




1. **Grasp your leg muscle at the outer mid-thigh** and **cleanse the area** with a new alcohol wipe.
2. **Push the needle into your leg muscle straight** in at a 90-degree angle.
3. **Inject the medication** by depressing the plunger in a slow and steady motion.
4. **Remove the needle** and wipe the site with the alcohol wipe.
5. May repeat dose every 5 minutes (**maximum 3 doses**) if ordered per protocol.

**Take the pills by mouth.**

a. 2 – Acetaminophen
b. 2 – Diphenhydramine

**Place all trash in the bag the pills came in** and take with you when you seek medical care. **Give the bag to the nurse or EMT**, so your doctor will know what medication you already took. They will properly dispose of the syringe and needles.

**Call 911** or have someone drive you to the emergency department.