

TZIELD (TEPLIZUMAB): GUIDE FOR HEALTHCARE PROFESSIONALS

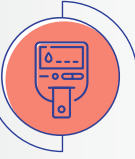
This guide is intended for Healthcare Professionals, Specialists prescribers (endocrinologists, diabetologists, pediatric endocrinologists), Nurses, Hospital's Pharmacists, , laboratory assistants, laboratory technicians, General Practitioners, and pediatricians, involved in the management of patients treated with teplizumab.

This guide contains important safety information Healthcare Professionals need to be aware of when treating patients with TZIELD (teplizumab). Before any prescription / administration of teplizumab to patients please refer to the SmPC/Product information for complete information.

In case of any suspected adverse reaction please report to the National Pharmacovigilance Centre (NPC) at Saudi Food and Drug Authority (SFDA):

- SFDA call center: 19999.
 - E-mail: npc.drug@sFDA.gov.sa
 - Website: <https://ade.sFDA.gov.sa>
- Also, you can report to SANOFI via
- +966-54-428-4797
 - KSA_Pharmacovigilance@sanofi.com

Tabel of Content

Objectives of Guide			
Mechanism of Action of TZIELD			Staging of Autoimmune T1D 
Preparing patients for their TZIELD infusion • Confirm Stage 2 patients • Laboratory parameters prior to infusion initiation • Vaccinations prior and after infusion • Pregnancy and lactation			Before & during TZIELD treatment 
Recommending dosing of TZIELD • Dosing regimen		Possible serious adverse reactions of TZIELD & How to mitigate them • Cytokine Release Syndrome • Lymphopenia • Serious infection • Hypersensitivity reaction	How to use TZIELD • Infusion preparation

1. OBJECTIVES OF THIS GUIDE

TZIELD (Teplizumab) is 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.

This Guide includes important information on administration of TZIELD that you should know before initiating TZIELD treatment. It is designed to support HCPs informing patient/legal representative/caregiver and in managing the possible serious adverse reactions associated with the use of TZIELD:

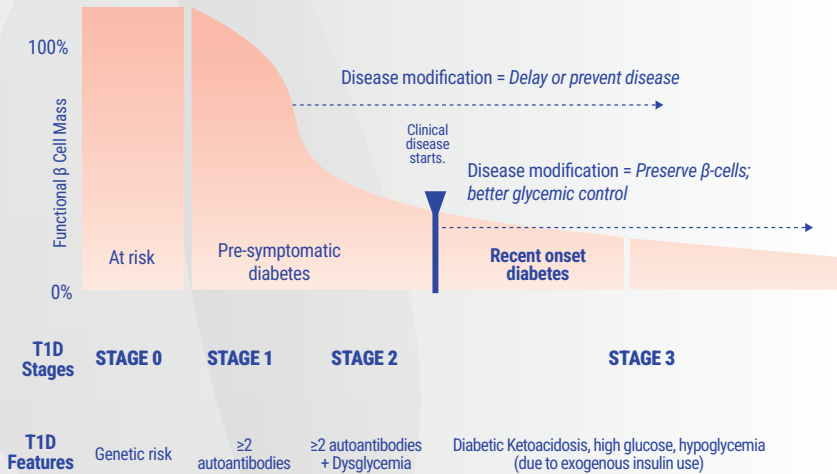
Important Safety Information related to TZIELD:

- **Cytokine Release Syndrome (CRS).**
- **Lymphopenia.**
- **Serious infection.**
- **Hypersensitivity reactions.**

For patients who are minors or without the capacity to make an informed decision, provide the information to their parents/legal representative/ caregiver and make sure they clearly understand it.

2. STAGING OF AUTOIMMUNE T1D

T1D Is a Progressive Autoimmune Condition Involving Loss of Beta Cell Function Over 3 Stages¹:



Stage 1 represents individuals who have developed two or more type 1 diabetes–associated islet autoantibodies but are normoglycemic.

Stage 2, like stage 1, includes individuals with two or more islet autoantibodies but whose disease has now progressed to the development of glucose intolerance, or dysglycemia, from loss of functional beta-cell mass. The 5-year risk of symptomatic disease at this stage is approximately 75%, and the lifetime risk approaches 100%¹.

Stage 3 represents manifestations of the typical clinical symptoms and signs of diabetes, which may include polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis (DKA), and others¹.

Reference:

1. Insel RA, et al. Diabetes Care. 2015; 38(10): 1964-1974

3. MECHANISM OF ACTION OF TEPLIZUMAB



Autoimmune therapy for Stage 2 T1D¹

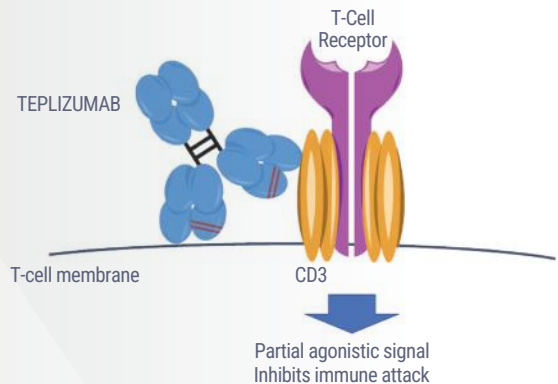
TZIELD is a CD3-directed monoclonal antibody that binds to CD3 antigens presented on the surface of T cells and delays the onset of Stage 3 T1D.

Mechanism of action¹

The mechanism may involve partial agonistic signaling and deactivation of autoreactive T cells that attack and destroy pancreatic beta cells.

Teplizumab:

- Does not cause depletion of T cells.
- Delivers partial agonistic signal and inhibits autoimmune attack on beta cells.
- Increases regulatory T cell function.
- Induces expansion of partially exhausted CD8+ T cells that are linked to preserved beta cell function in recently-diagnosed T1D patients¹ associated with slower loss of C-peptide following T1D diagnosis^{2,3}
- Partial agonistic signal leads to transient cytokine release responsible for mechanism-based side effects.



References:

1. Ramos, E.L. et al. N Engl J Med 2023;389:2151-61. Inhibits immune attack
2. Herold, KC, Diabetologia 2013 56(2): 391–400
3. Long SA, et al. Sci Immunol. 2016; 1(5):eaai7793.

4. BEFORE AND DURING TZIELD TREATMENT:

Ensure patient eligibility criteria before initiating Teplizumab:



Eligibility Criteria:

TZIELD is a CD3-directed monoclonal 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.



TZIELD is contraindicated in patients who have had severe hypersensitivity reactions, including anaphylaxis, to teplizumab or any of its excipients.

- TZIELD is not recommended in pregnant and lactating women.

- Confirm Stage 2 T1D
- Obtain a complete blood count and liver enzyme tests
- Check for active serious or chronic infection
- Administer all age-appropriate vaccinations prior to starting TZIELD

PREMEDICATION:

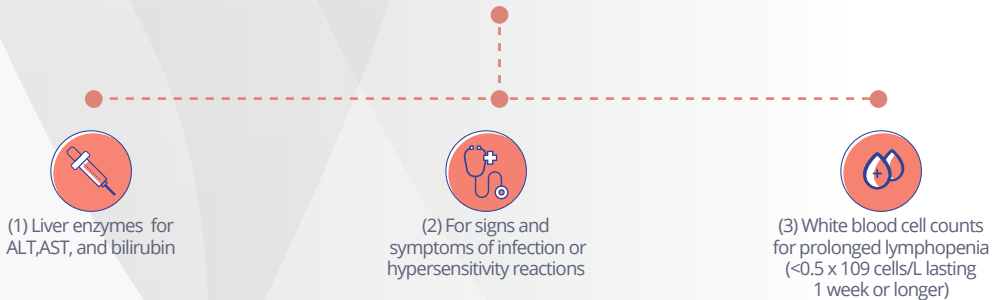
To mitigate Cytokine Release Syndrome (CRS), premedicate prior to TZIELD infusion for the first 5 days of dosing with:



Administer additional doses of premedication beyond day 5 if needed.

DURING MEDICATION:

Throughout the treatment course, monitor:



If CRS, serious infections, lymphopenia, and/or hypersensitivity reactions were to occur, see the Prescribing Information and next pages for management considerations.

5. PREPARING PATIENTS FOR THEIR TZIELD INFUSION

I. Confirm Stage 2 Patient

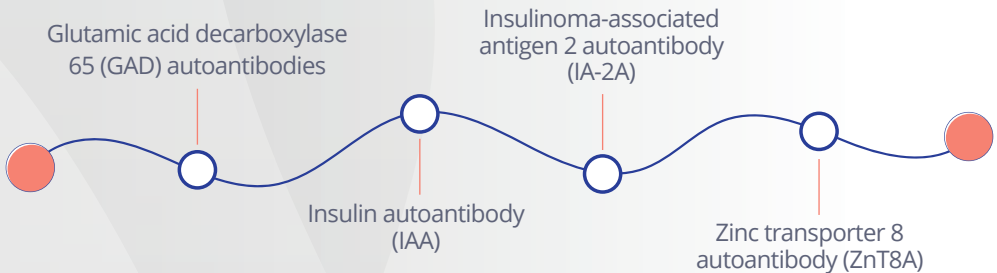
TZIELD is only for adult and pediatric patients 8 years of age and older who have a diagnosis of Stage 2 T1D.

Therefore **Stage 2 T1D should be confirmed by the following criteria:**



ICAs are not generally used for screening as they lack specificity and are technically challenging to detect.^{1,2}

- At least 2 positive pancreatic islet cell autoantibodies:



- Hyperglycemia using an oral glucose tolerance test (OGTT) or an alternative method as appropriate.
- Ensure the clinical history of the patient does not suggest type 2 diabetes.

References:

1. Peters A. J Fam Pract. 2021;70(6S):S47-52.
2. Winter WE, et al. J Appl Lab Med. 2022;7:197-205

II. Patient Considerations And Laboratory Evaluation Prior To Infusion Initiation

Prior to initiating TZIELD, obtain a complete blood count and liver enzyme tests.

Starting TZIELD is not recommended in patients with:

- Lymphocyte count less than 10^9 lymphocytes/L
- Hemoglobin less than 100 g/L
- Platelet count less than 150×10^9 platelets/L
- Absolute neutrophil count less than 1.5×10^9 neutrophils/L
- Elevated alanine aminotransferase (ALT) or aspartate aminotransferase (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 or cytomegalovirus
- Active serious infection or chronic active infection other than localized skin infections



III. Vaccinations Prior And After Infusion

The safety of immunization with live-attenuated vaccines in TZIELD-treated patients has not been studied. TZIELD may interfere with the immune response to vaccination and decrease vaccine efficacy.



Administer all age-appropriate vaccinations prior to starting TZIELD:

- Administer live-attenuated vaccines at least 8 weeks prior to treatment.
- Administer inactivated (killed) or mRNA vaccines at least 2 weeks prior to treatment.



Vaccination after the treatment

- Live-attenuated vaccines are not recommended up to 52 weeks after completion of treatment.
- Inactivated or mRNA vaccines are not recommended 6 weeks after completion of treatment.

IV. Pregnancy And Lactation

Pregnancy:

Patients should inform their healthcare provider of a known or suspected pregnancy as they should not receive TZIELD during pregnancy and at least 30 days before a planned pregnancy.



Lactation:

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



6. POSSIBLE SERIOUS ADVERSE REACTIONS OF TZIELD AND HOW TO MITIGATE

POSSIBLE INFUSION-RELATED ADVERSE REACTIONS	HOW TO MITIGATE THESE ADVERSE REACTIONS
Cytokine Release Syndrome (CRS) CRS has been observed in TZIELD-treated patients. Symptoms included: • Fever, • Nausea, • Fatigue, • Headache, • Myalgia, • Arthralgia, • Increased ALT, increased AST and increased total bilirubin These symptoms typically occurred during the first 5 days of treatment.	• To mitigate CRS Premedicate patients prior to teplizumab infusion for the first 5 days of dosing with: 1) a nonsteroidal anti-inflammatory drug (NSAID) or acetaminophen/paracetamol 2) an antihistamine, and/or 3) consider use of an antiemetic. Administer additional doses of premedication beyond day 5 if needed. • Monitor liver enzymes ALT, AST and bilirubin during treatment. • Discontinue treatment in patients who develop elevated ALT or AST 5 times ULN (upper-limit-normal) or bilirubin 3 times ULN • Treat symptoms of CRS with antipyretics, antihistamines, and/or antiemetics. • If severe CRS develops, consider temporarily pausing dosing for 1 day - 2 days (and administer the remaining doses to complete the full 14-day course on consecutive days) or discontinuing treatment. • Follow strictly instructions on the infusion preparation and the dosing regimen.
 inform patients on such signs and symptoms and if they occur, to urgently seek medical advice/ contact their treating HCPs: to receive an adequate treatment.	

POSSIBLE INFUSION-RELATED ADVERSE REACTIONS	HOW TO MITIGATE THESE ADVERSE REACTIONS
Lymphopenia TZIELD-related effects included lymphopenia. • For most patients treated with teplizumab who experience lymphopenia, lymphocyte levels began to recover after the fifth day of treatment and returned to pretreatment values within 2 weeks after treatment completion and without dose interruption	• Monitor white blood cell counts during the treatment period. • If prolonged severe lymphopenia ($<0.5 \times 10^9$ cells/L lasting one week or longer) develops, discontinue TZIELD. • Follow strictly the instructions on the infusion preparation and the dosing regimen
 Inform patients that you will be monitoring white blood cell counts, and if this is too low for a prolonged period of time TZIELD may have to be discontinued.	
Serious Infections Bacterial and viral infections have occurred in TZIELD-treated patients, including: • Gastroenteritis, • Cellulitis, • Pneumonia, • Abscess, and • Sepsis	• Use of TZIELD is not recommended in patients with active serious infection or chronic active infection other than localized skin infections. • Monitor patients for signs and symptoms of infection during and after TZIELD treatment. • If serious infection develops, treat appropriately, and discontinue TZIELD
 In case of infection symptoms inform patients to urgently seek medical advice/contact their treating HCPs to receive an adequate treatment.	
Hypersensitivity Reactions Acute hypersensitivity reactions, including: • serum sickness, • angioedema, • urticaria, • rash, • vomiting and • bronchospasm occurred in TZIELD-treated patients.	• TZIELD is contraindicated in patients who have had severe hypersensitivity reactions, including anaphylaxis, to teplizumab or any of its excipients. • If severe hypersensitivity reactions occur, discontinue use of TZIELD and treat promptly
 If such symptoms occur inform patients to seek medical attention promptly/contact their treating HCPs to receive an adequate treatment.	

7. RECOMMENDED DOSING FOR TZIELD

TZIELD is administered by IV infusion (over a minimum of 30 minutes) once daily for 14 consecutive days.



Once daily, consecutive 14-day course¹

If a planned infusion is missed, resume course by administering all remaining doses on consecutive days to complete the 14-day course.

Do not administer 2 doses on the same day.

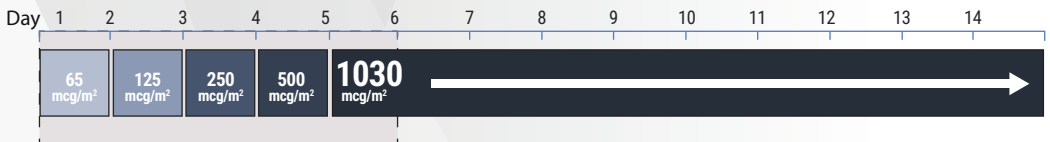


≥30-minute administration¹

Administer TZIELD by IV infusion for a minimum of 30 minutes, using a body surface area-based dosing.

The recommended TZIELD dosage for adults and pediatric patients aged 8 years and older uses body surface area (BSA)-based dosing and is administered according to the following regimen:

DOSING REGIMEN



Based on BSA dosing requirements, 2 vials may be needed for some individuals (BSA > 1.94m²) for days 5-14.

Reference:

1. Insel RA, et al. Diabetes Care. 2015; 38(10): 1964-1974

8. HOW TO USE TZIELD: INFUSION PREPARATION

TZIELD is supplied as a sterile, preservative-free, clear, and colorless solution in a 2 mg/2 mL, single-dose vial.

For detailed information regarding storage conditions refer to the product label.



TZIELD must be diluted prior to use.



- 1** Inspect TZIELD visually before use (the supplied solution is clear and colorless).
- Do not use TZIELD if particulate matter or coloration is seen.



- 2** Prepare TZIELD using aseptic technique. Each vial is intended for single dose only. Prepare a sterile glass vial with 18 mL of 0.9% Sodium Chloride Injection or polyvinylchloride (PVC) infusion bag with 18 mL of 0.9% Sodium Chloride Injection.



- 3** Remove 2 mL of TZIELD from the vial and slowly add to the 18 mL of 0.9% Sodium Chloride Injection. Mix gently by slowly inverting the vial or rocking the infusion bag. The resulting 20 mL diluted solution contains 100 mcg/mL of TZIELD.



- 4** Using an appropriately sized syringe (e.g., 5 mL), withdraw the volume of diluted TZIELD solution required for that day's calculated dose from the 100 mcg/mL solution.



- 5** Slowly add contents of the syringe containing the TZIELD dose to a 25 mL 0.9% Sodium Chloride Injection PVC infusion bag. Gently rock the infusion bag to ensure that the solution mixes sufficiently.
- Do not shake.

Important:

Based on BSA dosing requirements (e.g., $>1.94 \text{ m}^2$), 2 vials may be needed for days 5 through 14. To make sure the complete dose for each day is contained in 1 infusion bag:

- Prepare 2 diluted TZIELD solutions.
- Add the cumulative volume for the calculated dose to a single infusion bag.



6 Discard unused portion of remaining diluted TZIELD solution in the sterile glass vial or PVC infusion bag.

- The unused solution should not be used for another patient.



7 Start the TZIELD infusion within 2 hours of preparation. If not used immediately, store the infusion solution at room temperature [15°C to 30°C] and complete infusion within 4 hours of the start of preparation.

- Discard the infusion solution if not administered within 4 hours of preparation.



8 When the TZIELD infusion solution has been completely administered, infuse an additional volume of 0.9% sodium chloride solution for injection (i.e., normal saline) equal to the volume contained in the infusion tubing at the same constant rate as TZIELD infusion to ensure that all the medication has been given.