▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – TZIELD® (TEPLIZUMAB)

1 NAME OF THE MEDICINE

Teplizumab

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 2 mg of teplizumab in 2 mL of concentrated solution (2 mg/2 mL).

Teplizumab is a CD3-directed monoclonal antibody (humanised IgG1 kappa) produced in Chinese hamster ovary (CHO) cell line by recombinant DNA technology.

For the full list of excipients, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

Concentrated injection

Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Tzield is indicated to delay the onset of Stage 3 type 1 diabetes mellitus (T1D) in adult and paediatric patients aged 8 years and older with Stage 2 type 1 diabetes mellitus (see Section 5.1 Pharmacodynamic Properties – Clinical trials).

4.2 DOSE AND METHOD OF ADMINISTRATION

Tzield should be administered by a healthcare professional with access to appropriate medical support to manage potential severe adverse reactions.

Laboratory Evaluation and Vaccination Prior to Initiation

- Stage 2 T1D confirmed by:

- At least two positive pancreatic islet autoantibodies
- Dysglycaemia without overt hyperglycaemia

- Prior to initiating Tzield, a full blood count and liver enzyme tests should be obtained. Additionally, patients should be evaluated for active Epstein-Barr Virus (EBV) and Cytomegalovirus (CMV) infection, and an undetectable viral load should be confirmed prior to initiation.

- Use of Tzield is not recommended in patients with (see Section 4.4 Special Warnings and Precautions for Use):
  - Lymphocyte count less than 1.0 x 10^9 lymphocytes/L
  - Haemoglobin less than 100 g/L
  - Platelet count less than 100 x 10^9 platelets/L
  - Absolute neutrophil count less than 1.5 x 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 (EBV) or cytomegalovirus (CMV)
  - Active serious infection or chronic active infection other than localised skin infections

- All age-appropriate vaccinations should be administered prior to starting Tzield (see Section 4.4 Special Warnings and Precautions for Use).

Monitoring

Recommended monitoring during treatment with Tzield:

- Monitor patients for signs and symptoms of viral reactivation during Tzield treatment and for at least 2 months following the last infusion.
- Monitor lymphocyte count regularly during Tzield infusion and monitor for lymphocyte recovery following completion of the Tzield course.
- Monitor liver function and bilirubin during treatment.

Additional monitoring may be required based on clinical judgement.

Premedication

Premedication should be used prior to Tzield infusion for the first 5 days of dosing with: (1) a nonsteroidal anti-inflammatory drug (NSAID) or paracetamol, (2) an antihistamine, and (3) use of an antiemetic could be considered (see Section 4.4 Special Warnings and Precautions for Use). Additional doses of premedication should be administered if needed.

Dose

Tzield should be administered by intravenous infusion (over a minimum of 30 minutes), using a Body Surface Area (BSA) - based dosing, once daily for 14 consecutive days as follows:

- Day 1: 65 micrograms/m^2
- Day 2: 125 micrograms/m^2
- Day 3: 250 micrograms/m^2
- Day 4: 500 micrograms/m^2
- Days 5 through 14: 1030 micrograms/m^2

Missed dose(s)

If a planned Tzield infusion is missed, dosing should be resumed by administering all remaining doses on consecutive days to complete the 14-day treatment course.

Treatment discontinuation

Temporary treatment discontinuation may be required according to the severity of laboratory abnormalities. Based on clinical judgment, treatment should be paused if platelet count, neutrophil count, or haemoglobin level decreases significantly.

Dose interruption should not exceed 3 days. Dosing may be resumed by administering all remaining doses on consecutive days to complete the 14-day treatment course (e.g. if dosing is missed on Days 4 and 5, dosing may restart at Day 6 with the dosing level specified for Day 4).

Treatment should be permanently discontinued if any of the following occurs:

- Elevated liver enzymes (ALT or AST greater than 5 times ULN) or bilirubin greater than 3 times ULN
- Prolonged severe lymphopenia (< 0.5 x 10^9 lymphocytes/L lasting 1 week or longer)
- Clinically relevant (based on individual patient data as evaluated by the treating physician or paediatrician) decrease of platelet count, neutrophil count, or haemoglobin level for 3 consecutive days
- A serious infection develops
- Viral reactivation is confirmed

For additional information, see Section 4.4 Special Warnings and Precautions for Use and Section 4.8 Adverse Effects (Undesirable Effects)

Method of Administration

Tzield should be administered by intravenous infusion over a minimum of 30 minutes. Do not administer two doses on the same day.

For instructions for disposal of Tzield, see Section 6.6 Special Precautions for Disposal.

Preparations for intravenous administration

- Tzield must be diluted prior to use. This requires a two-step dilution process.
- In preparation for dilution, inspect Tzield visually before use (the supplied solution is clear and colourless). Do not use Tzield if particulate matter or colouration is seen.
- Prepare Tzield using aseptic technique. Each vial is intended for single dose only.
- Start the infusion immediately after dilution. If not used immediately, store the diluted solution for infusion (see Section 6.3 Shelf life).

Step 1: Initial dilution (1:10)

- Prepare 18 mL of sodium chloride 9 mg/mL (0.9%) solution for injection in a:
  - Sterile glass vial, or
  - Sterile polyvinylchloride (PVC)) with di-(2-ethylhexyl)phthalate (DEHP) infusion bag, or
  - Sterile syringe (polypropylene (PP) or polycarbonate (PC))
- Remove the cap from the vial – this is the preparation start time (see section 6.3).

  Based on BSA dosing requirements (e.g. > 1.94 m^2), 2 vials may be needed for days 5 through 14.

  In this case, to make sure the complete dose for each day is contained in 1 infusion bag or syringe:

  - Prepare 2 dilution solutions
  - Add the cumulative volume for the calculated dose to a single infusion bag or syringe
- Remove 2 mL of Tzield from the vial and slowly add to the 18 mL of sodium chloride 9 mg/mL (0.9%) solution for injection. Mix gently by slowly swirling the vial or rocking the infusion bag or syringe. The resulting 20 mL diluted solution contains 100 micrograms (mcg)/mL of teplizumab.

- Calculate patient's BSA using the Mosteller formula before treatment.

$$\textbf{BSA } (\textbf{m}^2) = \sqrt{(\text{Height (cm)} \times \text{Weight (kg)})/3600}$$

- Using the patient's BSA, calculate the dose based on treatment day (see section 4.2 – Dose (above)).

$$\text{Dose (x mcg)} = \text{Daily dosage level } \left(\frac{\text{x mcg}}{\text{m}^2}\right) \times \text{BSA } (\text{m}^2)$$

- Calculate the volume of 100 mcg/mL Tzield solution (prepared in Step 1) to

be further diluted in Step 2.

$$\textbf{Volume of initial dilution, 1:10 (mL)} = \frac{\text{Dose (x mcg)}}{\text{100 mcg/mL}}$$

Examples for initial dilution volume (Step 1):

Example 1:
For a BSA of 1.25 m^2 and the corresponding treatment dose for Day 3 of 250 mcg/m^2, the initial dilution volume is:

[(250 mcg/m^2) x (1.25 m^2)]/100 mcg/mL = 3.1 mL.

Example 2:
For a BSA of 1.70 m^2 and the corresponding treatment dose for Day 5 of 1030 mcg/m^2, the initial dilution volume is:

[(1030 mcg/m^2) x (1.70 m^2)]/100mcg/mL =17.5 mL.

Step 2: Final dilution

There are two different methods for IV administration of final dilution: infusion bag or syringe pump infusion. Use the appropriate calculation depending on the selected method.

- Infusion bag for IV administration:
  - 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 100mcg /mL solution (see Step 1: Initial dilution, 1:10).
  - Slowly add contents of the syringe containing the Tzield dose to a PVC with DEHP infusion bag containing 25 mL 9 mg/mL (0.9%) sodium chloride solution for injection. Gently rock the infusion bag to ensure that the solution mixes sufficiently. Do not shake.
  - Infusion administration has a minimum duration of 30 minutes. Rate may be slowed for patient's tolerability.

- Syringe (PP or PC) for IV infusion via syringe pump [Tzield concentration range 15 mcg/mL to 60 mcg/mL]:

  - Calculate the maximum volume that can be administrated for the calculated dose (based on treatment day, dose and patient BSA) using a minimum infusion concentration of 15 mcg/mL.

$$\textbf{Volume}_{\textbf{Infusion}}\textbf{(mL)} = \frac{\text{Dose (x mcg)}}{\text{Minimum infusion concentration 15 mcg/mL}}$$

    - Calculate the volume of saline to be added to the infusion syringe:

      a) If the calculated maximum volume to be administered is ≤ 60 mL:

$$\textbf{Volume}_{\textbf{Saline}}\textbf{(mL)} = \text{Volume}_{\text{Infusion}}\text{(mL)} - \text{Volume}_{\text{initial dilution, 1:10}}\text{ (mL)}$$

Example 1 for final dilution:

For a BSA of 1.25 m^2 and the corresponding treatment dose for Day 3 of 250 mcg/m^2, the calculated volume to be administered is:

[(250 mcg/m^2) x (1.25 m^2)]/15 mcg/mL = 20.8 mL

The volume of saline to be added to the infusion syringe:

20.8 mL – 3.1 mL = 17.7 mL

b) If the calculated maximum volume to be administered exceeds 60 mL – the maximum infusion volume is capped at 60 mL.

$$\textbf{Volume}_{\textbf{Saline}}\textbf{(mL)} = 60\text{ mL} - \text{Volume}_{\text{initial dilution, 1:10}}\text{ (mL)}$$

Example 2 for final dilution:
For a BSA of 1.70 m^2 and the corresponding treatment dose for Day 5 of 1030 mcg/m^2, the calculated volume to be administered is:

[(1030 mcg/m^2) x (1.70 m^2)]/15mcg/mL = 116.7 mL.

As the volume exceeds 60 mL, use 60 mL to calculate the volume of saline required. The volume of saline to be added to the infusion syringe:

60 mL – 14.5 mL = 45.5 mL

- Measure the appropriate volume of saline and transfer it to the infusion syringe.
- Using an appropriately sized syringe (e.g. 5 mL), withdraw the volume of diluted Tzield solution calculated above (see volume of initial dilution, 1:10) and add it to the infusion syringe.
- Gently rock the infusion syringe to ensure that the solution mixes sufficiently. Do not shake.
- Attach infusion syringe to a syringe pump. The syringe pump should support rates as low as 1 mL/hour.
- Run infusion with syringe pump – **do not manually push the syringe**. Calculate the infusion rate (to ensure a minimum of 30 minutes). Maximum infusion rate should be 2 mL/min (maximum 120 mL/hour). The actual rate will vary based on the volume of infusion, as shown below.

$$\textbf{Infusion rate (mL/minute)} = \frac{\text{Volume}_{\text{Infusion}}\text{(mL)}}{30\text{ minutes}}$$

Example 1:

Infusion rate: 20.8 mL / 30 minutes = 0.7 mL/min

Example 2:

Infusion rate: 60 mL / 30 minutes = 2 mL/min

- Infusion administration has a minimum duration of 30 minutes. Rate may be slowed for patient's tolerability.

A summary of the calculations for both examples is provided below:

Example 1								
Indication	**Treatment Day and Dose**	**BSA m^2**	**Patient Dose Tzield (mcg)**	**Initial Dilution Volume 1:10 (mL)**	**Saline Volume (mL)**	**Infusion Volume (mL)**	**Infusion Concentration (mcg/mL)**	**Infusion Rate 30 min (mL/min)**
Stage 2 T1D	Day 3 250 mcg/m^2	1.25 m^2	312.5 mcg	3.1 mL	17.7 mL	20.8 mL	15 mcg/mL	0.7 mL/min

Example 2								
Indication	**Treatment Day and Dose**	**BSA m^2**	**Patient Dose Tzield (mcg)**	**Initial Dilution Volume 1:10 (mL)**	**Saline Volume (mL)**	**Infusion Volume (mL)**	**Infusion Concentration (mcg/mL)**	**Infusion Rate 30 min (mL/min)**
Stage 2 T1D	Day 5 1030 mcg/m^2	1.70 m^2	1,751 mcg	17.5 mL	42.5 mL	60 mL	29.2 mcg/mL	2 mL/min

These steps may be followed if using a sterile glass vial for dilution preparation instead of a syringe (for IV infusion via syringe pump). An overfill should be considered as part of the calculations.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 List of Excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Cytokine Release Syndrome

Cytokine Release Syndrome (CRS) has been observed in clinical studies in patients treated with Tzield during the treatment period and through 28 days after the last administration (see Section 4.8 Adverse Effects (Undesirable Effects). CRS 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 Tzield treatment (see Section 4.8 Adverse Effects (Undesirable Effects)).

To mitigate CRS:

- antipyretics, antihistamines and/or antiemetics should be administered prior to Tzield treatment (see Section 4.2 Dose and Method of Administration).
- liver enzymes and bilirubin should be monitored during treatment, more frequently within the first week. Treatment should be discontinued in patients who develop elevated ALT or AST more than 5 times the upper limit of normal (ULN) or bilirubin more than 3 times ULN.
- symptoms of CRS should be treated with antipyretics, antihistamines and/or antiemetics. If severe CRS develops, temporarily pausing dosing for 1-2 days should be considered (and the remaining doses to complete the full 14-day course should be administered on consecutive days). If CRS does not improve or if CRS recurs despite the pause, discontinuing treatment may be warranted.

Serious infections

Bacterial and viral infections have occurred in patients treated with Tzield, including gastroenteritis, cellulitis, pneumonia, abscess, sepsis (see Section 4.8 Adverse Effects (Undesirable Effects)). Epstein-Barr virus (EBV) reactivation may occur in patients treated with Tzield. In patients with co-morbid conditions predisposing them to significant immunocompromise, clinical course of reactivation may present with increased severity.

Use of Tzield is not recommended in patients with active serious infection, laboratory or clinical evidence of acute infection with EBV or CMV, or chronic infection other than localised skin infections. Patients should be monitored for signs and symptoms of infection during and after Tzield treatment, including viral reactivation. If serious infection develops, appropriate treatment should be provided and Tzield should be discontinued.

Viral Reactivation

Prior to initiating treatment with Tzield, evaluate patients for active EBV and CMV infection and confirm an undetectable viral load. Regularly monitor lymphocyte counts and monitor patients for signs and symptoms of viral reactivation during treatment with Tzield and for at least 2 months following the last infusion. If viral reactivation is suspected, discontinue Tzield and obtain viral load promptly. If viral reactivation is confirmed, permanently discontinue Tzield (see Section 4.2 Dose and Method of Administration).

Serious, life-threatening cases of viral reactivation, including those caused by EBV or CMV, have been reported with Tzield. During and within 2 months of Tzield treatment, if a primary infection or reactivation of EBV or CMV occurs, it may present with increased severity, including EBV-associated lymphoproliferative disease and organ failure. Patients who are immunocompromised, including patients with Down syndrome, may be at increased risk. Most serious viral reactivation cases occurred in patients who continued Tzield despite persistent, severe lymphopenia.

Consider specialist advice on diagnostic testing, as some tests may be inaccurate in immunosuppressed patients. Consider specialist advice for the management of severe viral reactivation.

Lymphopenia

In clinical trials, 75% of patients treated with Tzield developed lymphopenia. For most patients treated with Tzield 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 (see Section 4.8 Adverse Effects (Undesirable Effects)).

White blood cell counts should be monitored during the treatment period. If prolonged severe lymphopenia ($<0.5 \times 10^9$ cells/L lasting 1 week or longer) develops, treatment should be permanently discontinued (see Section 4.8 Adverse Effects (Undesirable Effects)).

Hypersensitivity Reactions

Acute hypersensitivity reactions including serum sickness, angioedema, urticaria, rash, vomiting and bronchospasm occurred in patients treated with Tzield. Generalised cutaneous reactions and anaphylaxis have occurred in at least one patient (see Section 4.8 Adverse Effects (Undesirable Effects)). If severe hypersensitivity reactions occur, Tzield should be discontinued and treatment should be provided promptly.

Vaccinations

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

- All age-appropriate vaccinations should be administered prior to starting Tzield (see Section 4.2 Dose and Method of Administration).
- Inactivated or mRNA vaccinations are not recommended within the 2 weeks prior to starting treatment, during treatment, or up to 6 weeks after completion of treatment.
- Live-attenuated vaccinations are not recommended within the 8 weeks prior to starting Tzield treatment, during treatment, or up to 52 weeks after completion of treatment.

Glucose monitoring

Blood glucose as well as signs and symptoms of hypoglycaemia or hyperglycaemia should be monitored and diabetes managed according to current practice guidelines.

Other considerations

Patients must not have type 2 diabetes (T2D) or secondary dysglycaemia related to a condition other than T1D (e.g. diabetes secondary to medicinal products or surgery, monogenic diabetes).

Educational/Safety Advice Tools

Healthcare professionals involved in the management of patients treated with Tzield must be familiar with the guides available for the safe use of this product and inform patients about the potential risks associated with the use of Tzield.

- Guide for risk minimisation for Healthcare Professional: Healthcare Professional Guide
- Guide for risk minimisation for Patients: Patient Guide – to be provided to patients by healthcare professionals

Use in hepatic impairment

No studies have been performed in patients with hepatic impairment (See Section 5.2 Pharmacokinetic properties).

Use in renal impairment

No studies have been performed in patients with renal impairment (See Section 5.2 Pharmacokinetic properties).

Body weight

BSA-based dosing normalises the exposure to teplizumab across body weight.

Use in the elderly

Clinical studies of Tzield did not include patients 65 years of age and older.

Paediatric use

The safety and efficacy of Tzield in children younger than 8 years of age have not been established. No data are available. See Section 5.2 Pharmacokinetic Properties.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No drug interaction studies have been performed.

Tzield should be administered with caution in patients with concomitant medicinal products that are associated with significant liver abnormalities, cytopenias and other immune modulators.

Cytokine release syndrome accompanied by a slight and transient increase in IL-6 concentrations may occur with Tzield.

Tzield is not expected to have any relevant cytochrome P450 mediated drug-drug interactions.

Tzield may interfere with the immune response to vaccination (see section 4.4).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no clinical data available for teplizumab on the effects on fertility. Fertility and reproductive performance were unaffected in female and male mice treated with a surrogate anti-mouse CD3 antibody up to 20 mg/kg by SC administration.

Use in pregnancy (Category B3)

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. Tzield is not recommended during pregnancy.

An embryo-fetal toxicity study with a surrogate anti-mouse CD3 antibody up to 20 mg/kg by SC administration in mice showed an increase in post-implantation loss in the presence of maternal toxicity.

Although there are no data on teplizumab, monoclonal antibodies can be actively transported across the placenta, and Tzield may cause immunosuppression in the utero-exposed infant. To minimise exposure to a fetus, avoid use of Tzield during pregnancy and for at least 30 days prior to planned pregnancy.

In a pre- and postnatal development toxicity study in pregnant mice in which the murine surrogate antibody was administered every 3 days from gestation day 6 through lactation day 19 at doses of 0, 0.3, 3, or 20 mg/kg, no maternal toxicity or increased incidence of post-implantation loss was observed. There were no effects on infant growth and development that were attributable to the surrogate antibody. A lower percentage of motile sperm and a trend towards reduction in fertility was observed in the offspring of dams administered the surrogate antibody at 20 mg/kg. Reductions in T cell populations and increases in B cells (all doses) and a reduction in the adaptive immune response to keyhole limpet hemocyanin (KLH; on postnatal days 35 and 84) at 20 mg/kg were observed in the offspring. No treatment-associated

opportunistic infections were seen in the offspring. The surrogate antibody was present in the offspring serum at levels 1.5% or less than that of maternal serum at the high dose.

Women of childbearing potential

Females of childbearing potential should consider effective contraception during treatment and for 30 days after the last dose of treatment. Tzield is not recommended in women of childbearing potential not using contraception.

Use in lactation

It is unknown whether teplizumab is excreted in human milk. In a pre- and post-natal development toxicity study in mice, it was suggested that the surrogate antibody was present in the milk of lactating mice. A risk to the newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with Tzield and for 30 days after the last dose of treatment.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Tzield has a minor influence on the ability to drive and use machines. Fatigue has been reported in patients (see Section 4.8 Adverse Effects (Undesirable Effects))

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the Safety Profile

The most frequently reported adverse reactions were lymphopenia (75%), leukopenia (58%), neutropenia (37%), and rash (36%). The most frequent serious adverse reaction was cytokine release syndrome (0.9%). Other serious adverse reactions included alanine aminotransferase increased (0.2%), aspartate aminotransferase increased (0.2%), lymphopenia (0.2%), neutropenia (0.2%), and infection (0.2%).

Tabulated List of Adverse Reactions

The adverse reactions occurring in patients in the pooled safety analysis of clinical studies and post-marketing setting are shown in Table 1 per MedDRA System Organ Class presented by frequency categories: very common: (≥1/10), common: (≥1/100 to <1/10), uncommon: (≥1/1000 to <1/100), rare: (≥1/10,000 to <1/1000), very rare: (<1/10,000), not known: (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 1 - Adverse reactions

System Organ Class	Frequency			
	Very common	**Common**	**Uncommon**	**Not known**
Infections and infestations			Infections[1]	Epstein-Barr virus reactivation
Blood and lymphatic system disorders	Lymphopenia, Thrombocytopenia Leukopenia, Neutropenia, Haemoglobin decreased	Eosinophilia		
Immune system disorders		Cytokine release syndrome	Hypersensitivity[1]	
Nervous system disorders	Headache			
Gastrointestinal disorders	Vomiting, Nausea	Diarrhoea, Abdominal pain		
Hepatobiliary disorders	Alanine aminotransferase increased, Aspartate aminotransferase increased	Bilirubin increased		
Skin and subcutaneous tissue disorders	Rash, Pruritus	Rash maculopapular, Rash pruritic, Urticaria, Skin exfoliation		
General disorders and administration site conditions	Pyrexia Fatigue	Chills		Pain, Illness

[1] Reported as serious – see "Description of selected adverse reactions".

Common Adverse Events

Table 2 presents common treatment-emergent adverse events (TEAEs) that occurred in ≥ 5% subjects in either the teplizumab group or the placebo group in Study TN-10.

Table 2 - Summary of TEAEs occurring in >5% subjects in any treatment group by MedDRA SOC and PT (Safety population)

SOC	**PT**	**Teplizumab** N=44	**Placebo** N=32	**Total** N=76
		n (%)	n (%)	n (%)
Subjects with at least 1 TEAE		43 (97.7)	22 (68.8)	65 (85.5)

SOC	PT	Teplizumab N=44	Placebo N=32	Total N=76
Blood and lymphatic system disorders		33 (75.0)	4 (12.5)	37 (48.7)
	Leukopenia	9 (20.5)	0	9 (11.8)
	Lymphopenia	32 (72.7)	2 (6.3)	34 (44.7)
	Neutropenia	3 (6.8)	1 (3.1)	4 (5.3)
Infections and Infestations		23 (52.3)	8 (25.0)	31 (40.8)
	Nasopharyngitis	7 (15.9)	2 (6.3)	9 (11.8)
	Pneumonia	4 (9.1)	1 (3.1)	5 (6.6)
	Sinusitis	4 (9.1)	1 (3.1)	5 (6.6)
	Upper respiratory tract infection	4 (9.1)	1 (3.1)	5 (6.6)
Skin and subcutaneous tissue disorders		20 (45.5)	3 (9.4)	23 (30.3)
	Rash	6 (13.6)	0	6 (7.9)
	Rash pruritic	7 (15.9)	0	7 (9.2)
Nervous system disorders		9 (20.5)	5 (15.6)	14 (18.4)
	Headache	5 (11.4)	3 (9.4)	8 (10.5)
Gastrointestinal disorders		7 (15.9)	3 (9.4)	10 (13.2)
	Vomiting	2 (4.5)	2 (6.3)	4 (5.3)
Respiratory, thoracic and mediastinal disorders		7 (15.9)	1 (3.1)	8 (10.5)
	Bronchospasm	3 (6.8)	0	3 (3.9)
	Cough	3 (6.8)	0	3 (3.9)
Vascular disorders		4 (9.1)	2 (6.3)	6 (7.9)
	Hypertension	4 (9.1)	1 (3.1)	5 (6.6)
Hepatobiliary disorders	Hyperbilirubinaemia	0	2 (6.3)	2 (2.6)

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term, SOC=Systems Organ Class, TEAE=treatment-emergent adverse event

Description of Selected Adverse Reactions

Cytokine Release Syndrome (CRS)

In Study TN-10, CRS was reported in 2% of patients treated with Tzield.

In the pool of 7 clinical trials, 6% of patients treated with Tzield developed CRS. In 14% of these patients, CRS was reported as serious (see Section 4.4 Special Warnings and Precautions

for Use). Liver transaminase elevations were observed more frequently in patients treated with Tzield who experienced CRS.

Serious Infections

In Study TN-10, serious infections (cellulitis, gastroenteritis, pneumonia, wound infection) were reported in 9% of patients treated with Tzield.

In the pool of 7 clinical studies, serious infections were reported in 3.1% of patients treated with Tzield, including gastroenteritis, cellulitis, pneumonia, abscess, sepsis, and infectious mononucleosis.

Lymphopenia

In Study TN-10, lymphopenia was reported in 73% of patients treated with Tzield. The average lymphocyte count nadir occurred at Day 5 of treatment, with recovery and return to baseline by Week 6 (see Section 4.4 Special Warnings and Precautions for Use).

In the pool of 7 clinical studies, severe lymphopenia ($< 0.5 \times 10^9$ cells/L) lasting 1 week or longer occurred in 2% of patients treated with Tzield and 0.5% of patients permanently discontinued treatment because of lymphopenia.

Rash and Hypersensitivity Reactions

Hypersensitivity reactions were reported with Tzield in Study TN-10. Serum sickness was observed in 2% of patients treated with Tzield

In the pool of 7 clinical trials of patients:

- Anaphylaxis (with hypoxia and bronchospasm) was observed in one patient treated with Tzield who was hospitalised.
- Angioedema (periorbital and facial) was observed in 0.2% patients treated with Tzield, compared to 0% of patients in the control group.
- Peripheral and generalised oedema was reported in 1.2% of patients treated with Tzield and 0.3% of patients in the control group.
- Rash was observed in 36% of patients treated with Tzield compared to 8% of patients in the control group. The majority of events of rash observed with Tzield treatment were not serious and resolved without intervention; although 0.3% (2/1008) of patients treated with Tzield had a serious rash compared to 0% (0/356) of patients in the placebo group.
- Urticaria was reported in 2.7% of patients treated with Tzield and in 1.1% of patients in the control group.
- Hypersensitivity reactions were reported in 1% of patients treated with Tzield. Less than 0.1% of patients treated with Tzield had a serious hypersensitivity reaction.

Haemoglobin Decreased and Thrombocytopenia

In the pool of 7 clinical trials of patients, haemoglobin decreased was reported in 23% of patients treated with Tzield and thrombocytopenia was reported in 17% of patients treated with Tzield; recovery occurred within 2 to 4 weeks of treatment. In clinical trials, 1.2% of patients treated with Tzield discontinued treatment due to haemoglobin less than 85 g/L (or a decrease of more than 20 g/L to a value less than 100 g/L), and 1% discontinued Tzield due to platelet count less than 50 x 10^9 platelets/L.

Liver Enzyme and Bilirubin Elevations

Liver enzyme and bilirubin elevations were observed in patients treated with Tzield, both in the context of CRS and in patients without CRS. On laboratory analysis, 7.8% of patients treated with Tzield experienced a peak ALT more than 3 times the ULN. For AST, 5.3% of patients treated with Tzield experienced a peak AST more than 3 times the ULN. Most liver enzyme elevations were transient and resolved 1-2 weeks after treatment.

Immunogenicity

The observed incidence of anti-drug antibodies (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies.

In the placebo-controlled study in patients aged 8 years of age and older with Stage 2 type 1 diabetes (Study TN-10) (see Section 5.1 Pharmacodynamic Properties – Clinical Trials), approximately 57% of patients treated with Tzield developed anti-teplizumab antibodies, 46% of whom developed neutralising antibodies.

Based on the available data, no definitive conclusion can be made to characterise the effects of ADA on pharmacokinetics, pharmacodynamics, or effectiveness of Tzield.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems (Australia).

4.9 OVERDOSE

There is no clinical experience with overdose with Tzield.

There is no known specific antidote for Tzield overdose. In the event of overdose, monitor the patient for any signs or symptoms of adverse reactions and institute appropriate symptomatic treatment immediately. Clinical judgement should be applied.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: other drugs in diabetes, ATC code: A10XX01.

Mechanism of action

Teplizumab preserves beta cell function by binding to CD3 (a cell surface antigen present on T lymphocytes) and delays the onset of Stage 3 T1D in Stage 2 patients. The mechanism may involve partial agonistic signalling 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.

Pharmacodynamic effects

Clinical studies have shown that teplizumab binds to CD3 molecules on the surface of both CD4+ and CD8+ T cells during treatment, with internalisation of the teplizumab/CD3 complex from the surface of T cells. Pharmacodynamic effects include lymphopenia in the absence of depletion of T cells with a nadir on the 5th day of dosing, during a 14-day course of Tzield treatment (see Section 4.4 Special Warnings and Precautions for Use). Teplizumab exposure-response relationship and time course of pharmacodynamic response for the safety and effectiveness of teplizumab have not been fully characterised.

Clinical Trials

The effectiveness of Tzield was investigated in the following clinical study:

Study TN-10

A randomised, double-blind, event-driven, placebo-controlled study in 76 patients, 8 to 49 years of age with Stage 2 type 1 diabetes (T1D). Stage 2 T1D was defined as having both of the following:

1. Two or more of the following pancreatic islet autoantibodies (positive on two occasions):
    - 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. Dysglycaemia on oral glucose tolerance testing

Study participants were required to have a family history of type 1 diabetes mellitus. Patients without a relative with type 1 diabetes mellitus were not studied. In this study, patients were randomised 1:1 to receive Tzield or placebo once daily by intravenous infusion for 14 days. The 2 treatment groups were:

- Group 1: Daily intravenous doses of 51micrograms/m^2,103micrograms/m^2,207 micrograms/m^2, and 413 micrograms/m^2 on study days 0 to 3, respectively, and 1 dose of 826 micrograms/m^2 on each of study days 4 to 13. The total dose for the 14-day course was approximately 9034 micrograms/m^2.
- Group 2: Intravenous placebo only

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 Section 4.2 Dose and Method of Administration). The primary efficacy endpoint in this study was the time from randomisation to development of Stage 3 T1D diagnosis.

Baseline Patient Characteristics

In this study, 45% were female and the median age was 14 years (72% were <18 years old). Patients' characteristics are displayed in Table 3.

Table 3 - Baseline age characteristics of adult and paediatric patients 8 years of age and older with Stage 2 Type 1 Diabetes (Study TN-10)[1]

	Tzield N=44	Placebo N=32
Age Group		
≥ 18 Years	34%	19%
< 18 years	66%	81%
Paediatric Age Group Quartiles		
8 to <11 years	21%	25%
11 to <14 years	27%	31%
14 to <18 years	18%	25%

[1] Intent to treat (ITT) population

Baseline Disease Characteristics

Table 4 displays the baseline disease characteristics in Study TN-10.

Table 4 - Baseline disease characteristics of adult and paediatric patients 8 years of age and older with Stage 2 Type 1 Diabetes (Study TN-10)[1]

	Tzield N=44	Placebo N=32
Glucose, mmol/L		
median (min, max)	9.2 (6.4, 11.5)	8.6 (5.7, 11.1)
OGTT 30 minutes, median (min, max)	8.9 (5.5, 13.2)	9.2 (6.7, 12.4)
OGTT 60 minutes, median (min, max)	10.3 (5.4, 13.6)	9.6 (4.3, 12.9)

	Tzield N=44	Placebo N=32
OGTT 90 minutes, median (min, max)	9.7 (5.4, 13.4)	8.8 (4.6, 13.6)
OGTT 120 minutes, median (min, max)	8.4 (4.8, 13.3)	8.0 (4.5, 12.1)
HbA1c, %		
median (min, max)	5.2 (4.6, 6.1)	5.3 (4.3, 5.6)
HLA-DR3/DR4		
Both DR3 and DR4	25%	22%
DR3 only	23%	25%
DR4 only	36%	44%
Neither DR3 nor DR4	11%	9%
Not analysed	5%	0
Autoantibody type positive		
GAD65	91%	88%
IAA	43%	34%
IA-2A	59%	75%
ICA	66%	88%
ZnT8	73%	75%
Autoantibodies Positive (N)		
1	2%	0
2	27%	22%
3	25%	16%
4	27%	44%
5	18%	19%

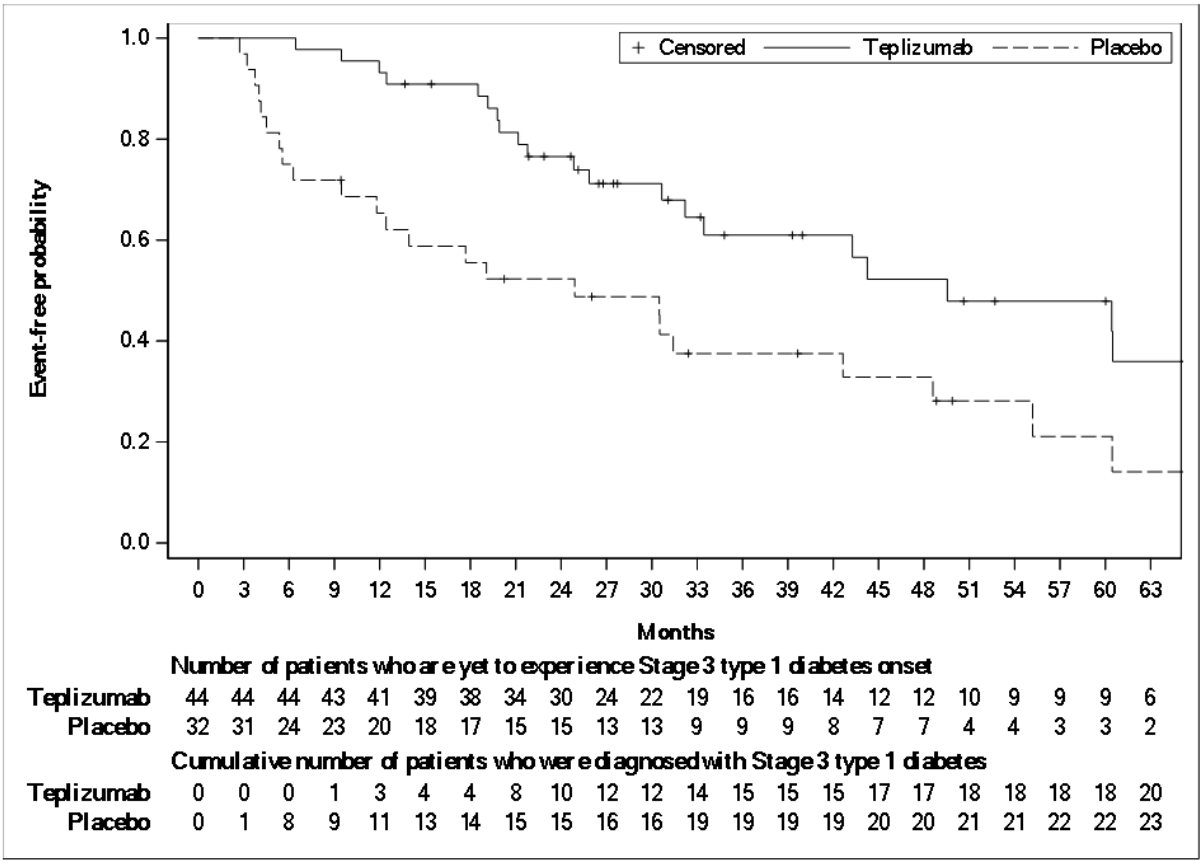
[1] Intent to treat (ITT) population [2] The glucose data are area under the time-concentration curve (AUC) values from the oral glucose tolerance test. Abbreviations: HbA1c=haemoglobin A1c, SD=standard deviation, HLA = human leukocyte antigen. GAD65=glutamic acid decarboxylase 65 (GAD) autoantibody, IAA=insulin autoantibody, IA-2A=insulinoma-associated antigen 2 autoantibody, ZnT8=zinc transporter 8 autoantibody, ICA=islet cell autoantibody.

Efficacy Results

In Study TN-10, Stage 3 type 1 diabetes was diagnosed in 20 (45%) of the patients treated with Tzield and in 23 (72%) of the patients treated with placebo. A Cox proportional hazards model, stratified by age and oral glucose tolerance test status at randomisation, demonstrated that the median time from randomisation to Stage 3 T1D 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 T1D, 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 T1D in adult and paediatric patients 8 years of age and older with Stage 2 T1D by treatment group (Study TN-10)[1]



[1] ITT population

5.2 PHARMACOKINETIC PROPERTIES

Steady state concentrations of teplizumab are not expected to be achieved during the 14-day course of Tzield.

Absorption

There is no information about absorption since Tzield is administered intravenously.

Distribution

No protein binding studies were conducted as teplizumab is a monoclonal antibody.

Metabolism

Teplizumab is expected to be metabolised into small peptides by catabolic pathways.

Elimination

The apparent elimination half-life of teplizumab is approximately 3 days.

Special Populations

Age

No clinically significant differences in the pharmacokinetics of teplizumab were observed based on age (8 to 35 years old).

Gender

No clinically significant differences in the pharmacokinetics of teplizumab were observed based on gender.

Race

No clinically significant differences in the pharmacokinetics of teplizumab were observed based on racial groups (White, Asian).

Paediatric

The pharmacokinetics of teplizumab in children younger than 8 years of age have not been established.

Hepatic Impairment

Specific studies to evaluate the pharmacokinetics of teplizumab in patients with hepatic impairment have not been performed.

Renal Impairment

Specific studies to evaluate the pharmacokinetics of teplizumab in patients with renal impairment have not been performed.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No studies have been performed to assess the genotoxic, including mutagenic, potential of teplizumab. As an antibody, teplizumab is not expected to interact directly with DNA or other chromosomal material.

Carcinogenicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Dibasic sodium phosphate
Monobasic sodium phosphate mononhydrate
Polysorbate 80
Sodium chloride
Water for injections

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, Tzield should not be mixed with other medicinal products. Do not add or simultaneously infuse other medicinal products through the same intravenous line. This medicinal product should be prepared and administered as instructed in Section 4.2 Dose and Method of Administration and Section 6.6 Special Precautions for Disposal.

Incompatible materials:

- Ethylene-propylene copolymer (EPC), polypropylene (PP), polyethylene (PE), and polyolefin (PO) blend IV infusion bags
- Light protected infusion sets

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

Diluted medicinal product

IV infusion bags

Chemical, physical and microbial in-use stability has been demonstrated for 6 hours at ambient temperature (15°C to 25 °C).

To reduce microbiological hazard, use as soon as practicable after preparation. If not used immediately, the diluted solution should not be stored longer than 6 hours at ambient temperature (15°C to 25 °C).

Syringe-based infusions

Chemical, physical and microbial in-use stability has been demonstrated for 12 hours under refrigerated conditions (2 °C to 8 °C), followed by no more than 6 hours at ambient temperature (15 °C to 25 °C).

To reduce microbiological hazard, use as soon as practicable after preparation. If not used immediately, the diluted solution should not be stored longer than 12 hours under refrigerated

condition (2 °C to 8 °C), followed by no more than 6 hours at ambient temperature (15°C to 25 °C).

Tzield is for single use in one patient only. Discard any residue.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in a refrigerator (2°C to 8°C). Do not freeze or shake the vials.

Keep the vial in the outer carton in order to protect from light. Store upright.

For storage conditions after dilution of the medicinal product, see Section 6.3 Shelf Life.

6.5 NATURE AND CONTENTS OF CONTAINER

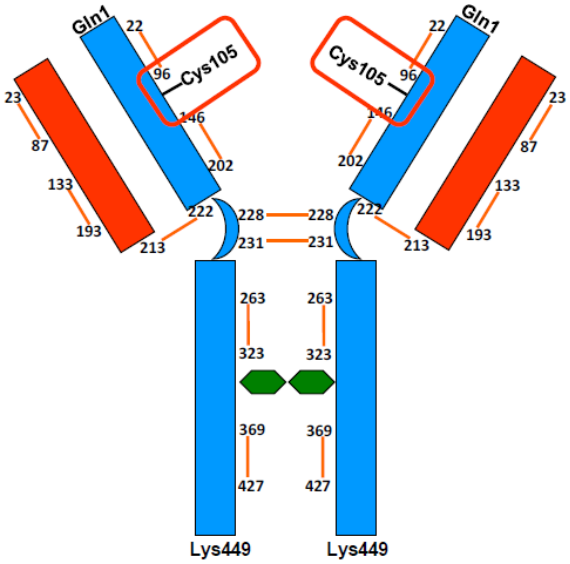
Tzield is supplied in a 2 mL Type 1 borosilicate glass vial with a butyl rubber stopper and an aluminium seal with a coloured polypropylene flip-off cap. Pack size of 1 vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



A schematic representation of the teplizumab antibody molecule showing the 16 disulfide bonds, the unpaired cysteine residues at position 105 in the heavy chain (HC), pyroglutamate formation at Gln1 of the HC, and C-terminal Lys449 in the HC.

Teplizumab consists of 2 identical light chain (LC) polypeptides of relative molecular weight (23,305 Dalton) and 2 identical heavy chain (HC) polypeptides of relative molecular weight (49,612 Dalton). These relative molecular weights are calculated from the theoretical amino acid sequences based on the cDNA sequences. Each HC polypeptide contains a single site for N linked glycosylation site at Asn299, which is modified with an oligosaccharide of approximately 1,458 Dalton, yielding an overall molecular weight of 148,750 Dalton for the teplizumab molecule. Teplizumab exhibits a high degree of C-terminal lysine cleavage (~95% by peptide mapping analysis) corresponding to a total molecular weight of 145,578 Dalton.

CAS number

876387-05-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicine)

8 SPONSOR

sanofi-aventis australia pty ltd
Level 23, Tower 3
300 Barangaroo Ave
Barangaroo NSW 2000
Toll Free Number (medical information): 1800 818 806
E-mail: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

21 May 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	New document