PACKAGE INSERT – Tzield® - Concentrated injection Vial

NAME OF THE MEDICINE

Teplizumab

DOSAGE FORM

Concentrated injection

METHOD OF PREPARATION

- 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 administered 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.

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 m²**	**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/m²	1.25 m²	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 m²**	**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

IN-USE STORAGE CONDITIONS

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.

SPONSOR

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