ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Teizeild 1 mg/mL concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL of concentrate for solution for infusion contains 1 mg of teplizumab.

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

Teplizumab is a monoclonal antibody (humanised IgG1 kappa) produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

Excipients with known effect

Each vial contains 7.45 mg of sodium and 0.10 mg of polysorbate 80.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate)

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Teizeild is indicated to delay the onset of stage 3 type 1 diabetes (T1D) in adult and paediatric patients 8 years of age and older with stage 2 T1D.

4.2 Posology and method of administration

Teizeild 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

- Prior to initiating Teizeild, a complete blood count and liver enzyme tests should be obtained.

- Use of Teizeild is not recommended in patients with (see section 4.4):
    - 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 initiating Teizeild (see section 4.4 for detailed guidance).

Premedication

Premedication should be used prior to Teizeild 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). Additional doses of premedication should be administered if needed.

Posology

Teizeild 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: 1 030 micrograms/m^2

Missed dose(s)
If a planned Teizeild 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:
- 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 (physician´s decision based on the individual patient´s data) decrease of platelet count, neutrophil count, or haemoglobin level for 3 consecutive days
- A serious infection develops

For additional information, see sections 4.4 and 4.8.

Special populations

Elderly
Clinical studies did not include elderly patients (65 years of age and older).

Renal impairment
No studies have been performed in patients with renal impairment (see section 5.2).

Hepatic impairment
No studies have been performed in patients with hepatic impairment (see section 5.2).

Body weight
BSA-based dosing is required to normalise the exposure of Teizeild across body weight (see Posology and section 5.2).

Paediatric population
The safety and efficacy of Teizeild in children younger than 8 years of age have not been established.

Method of administration

Teizeild should be administered by intravenous infusion over a minimum of 30 minutes.
Two doses should not be administered on the same day.

For instructions on preparation of the medicinal product before administration, see section 6.6 and at the end of the package leaflet.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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 teplizumab during the treatment period and through 28 days after the last administration (see section 4.8). 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 treatment (see section 4.8).

To mitigate CRS:
- antipyretics, antihistamines and/or antiemetics should be administered prior to treatment (see section 4.2).
- 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 Teizeild, including gastroenteritis, cellulitis, pneumonia, abscess, sepsis (see section 4.8). Use of Teizeild is not recommended in patients with active serious infection or chronic infection other than localised skin infections. Patients should be monitored for signs and symptoms of infection during and after treatment. If serious infection develops, appropriate treatment should be provided and Teizeild should be discontinued.

Lymphopenia

In clinical studies, 75% of patients treated with Teizeild developed lymphopenia. For most 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 (see section 4.8).

White blood cell counts should be monitored during the treatment period. If prolonged severe lymphopenia (< 0.5 x 10^9 cells/L lasting 1 week or longer) develops, treatment should be discontinued (see section 4.8).

Hypersensitivity reactions

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

Vaccinations

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

- All age-appropriate vaccinations should be administered prior to starting Teizeild (see section 4.2).
- Inactivated or mRNA vaccinations are not recommended within the 2 weeks prior to 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 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 Teizeild must be familiar with the guides available for the safe use of this medicinal product and inform patients about the potential risks associated with the use of Teizeild.

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

Excipients with known effect

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'. Teizeild is administered in 0.9% sodium chloride intravenous solution (see section 6.6).

Polysorbate 80
This medicinal product contains 0.10 mg of polysorbate 80 in each vial which is equivalent to 0.05 mg/mL. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No drug interaction studies have been performed.

Teizeild 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 Teizeild.

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

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential have to use effective contraception during treatment with teplizumab and for 30 days after the last dose of treatment. Teizeild is not recommended in women of childbearing potential not using contraception.

Pregnancy

There are no available data from the use of teplizumab in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Teizeild is not recommended during pregnancy.

Breast-feeding

It is unknown whether teplizumab is excreted in human milk. Toxicological data in animals suggest excretion of teplizumab in milk of lactating mice (see section 5.3). A risk to the newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with Teizeild and for 30 days after the last dose of treatment.

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 (see section 5.3).

4.7 Effects on ability to drive and use machines

Teizeild has a minor influence on the ability to drive and use machines. Fatigue has been reported (see section 4.8).

4.8 Undesirable effects

Summary of 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: (≥ 1/1 000 to < 1/100), rare: (≥ 1/10 000 to < 1/1 000), 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 maculo-papular, 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".

Description of selected adverse reactions

Cytokine release syndrome (CRS)
In study TN-10, CRS was reported in 2% of patients treated with Teizeild.

In the pool of 7 clinical studies, 6% of patients treated with Teizeild developed CRS. In 14% of these patients, CRS was reported as serious (see section 4.4). Liver transaminase elevations were observed more frequently in patients treated with Teizeild who experienced CRS.

Serious infections

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

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

Lymphopenia
In study TN-10, lymphopenia was reported in 73% of patients treated with Teizeild. The average lymphocyte count nadir occurred at day 5 of treatment, with recovery and return to baseline by week 6 (see section 4.4).

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

Rash and hypersensitivity reactions
Hypersensitivity reactions were reported with Teizeild in study TN-10. Serum sickness was observed in 2% of patients treated with Teizeild.

In the pool of 7 clinical studies of patients:

- Anaphylaxis (with hypoxia and bronchospasm) was observed in one patient treated with Teizeild who was hospitalised.
- Angioedema (periorbital and facial) was observed in 0.2% patients treated with Teizeild,
- Peripheral and generalised oedema was reported in 1.2% of patients treated with Teizeild.
- Rash was observed in 36% of patients treated with Teizeild. 0.3% of patients treated with Teizeild had a serious rash.
- Urticaria was reported in 2.7% of patients treated with Teizeild.
- Hypersensitivity reactions were reported in 1% of patients treated with Teizeild. Less than 0.1% of patients treated with Teizeild had a serious hypersensitivity reaction.

Haemoglobin decreased and thrombocytopenia
In the pool of 7 clinical studies, haemoglobin decreased was reported in 23% of patients treated with Teizeild and thrombocytopenia was reported in 17% of patients treated with Teizeild; recovery occurred within 2 to 4 weeks of treatment. In clinical studies, 1.2% of patients treated with Teizeild 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 Teizeild 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 Teizeild, both in the context of CRS and in patients without CRS. On laboratory analysis, 7.8% of patients treated with Teizeild experienced a peak ALT more than 3 times the ULN. For AST, 5.3% of patients treated with Teizeild 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 T1D (study TN-10) (see section 5.1), approximately 57% of patients treated with Teizeild developed treatment emergent 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 Teizeild.

Paediatric population

Immunogenicity data in children younger than 8 years of age have not been established.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

4.9 Overdose

There is no clinical experience with overdose with teplizumab.

There is no known specific antidote for Teizeild overdose. In the event of overdose the patient should be monitored for any signs or symptoms of adverse reactions and all appropriate measures should be taken immediately. Clinical judgement should be applied.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: other drugs in diabetes, ATC Code: A10XX01

Mechanism of action

Teplizumab binds to CD3 (a cell surface antigen present on T lymphocytes) and delays disease progression in patients with stage 2 T1D. The mechanism may involve partial agonistic signalling leading to deactivation of autoreactive CD8+ T lymphocytes and reduced immune-mediated beta-cell destruction. Teplizumab leads to an increase in the proportion of CD8+ T cells with signs of exhaustion 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 transient lymphopenia with a reduction in circulating T cells with a nadir on the 5th day of dosing, during a 14-day course of teplizumab treatment (see section 4.4). Teplizumab exposure-response relationship and time course of pharmacodynamic response for the safety and effectiveness of teplizumab have not been fully characterised.

Target patient population

Teplizumab is indicated in adult and paediatric patients 8 years of age and older who have a diagnosis of stage 2 T1D.

Stage 2 T1D confirmed by:
- At least two positive pancreatic islet autoantibodies
- Dysglycaemia without overt hyperglycaemia

Clinical efficacy and safety

The effectiveness of teplizumab 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 T1D. Stage 2 T1D 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 (ZnT8)
    - Islet cell autoantibody (ICA)

2. Dysglycaemia on oral glucose tolerance testing

In this study, patients were randomised 1:1 to receive teplizumab or placebo once daily by intravenous infusion for 14 days. The 2 treatment groups were:

- Group 1: Daily intravenous doses of 51 micrograms/m^2, 103 micrograms/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 9 034 micrograms/m^2.
- Group 2: Intravenous placebo only.

Patients in the teplizumab group had a total drug exposure that was comparable to the total drug exposure achieved with the recommended total teplizumab dose (see section 4.2*).* 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 2.

Table 2. Baseline characteristics of adult and paediatric patients 8 years of age and older with stage 2 T1D (Study TN-10)[1]

	Teplizumab 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%
Glucose, mg/dL[2]		
median (min, max)	165 (115, 207)	154 (103, 200)
OGTT 30 minutes, median (min, max)	161 (99, 237)	165 (121, 223)
OGTT 60 minutes, median (min, max)	186 (97, 244)	173 (77, 233)
OGTT 90 minutes, median (min, max)	175 (98, 242)	159 (82, 244)
OGTT 120 minutes, median (min, max)	152 (87, 240)	144 (81, 217)
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%

	Teplizumab N=44	Placebo N=32
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%

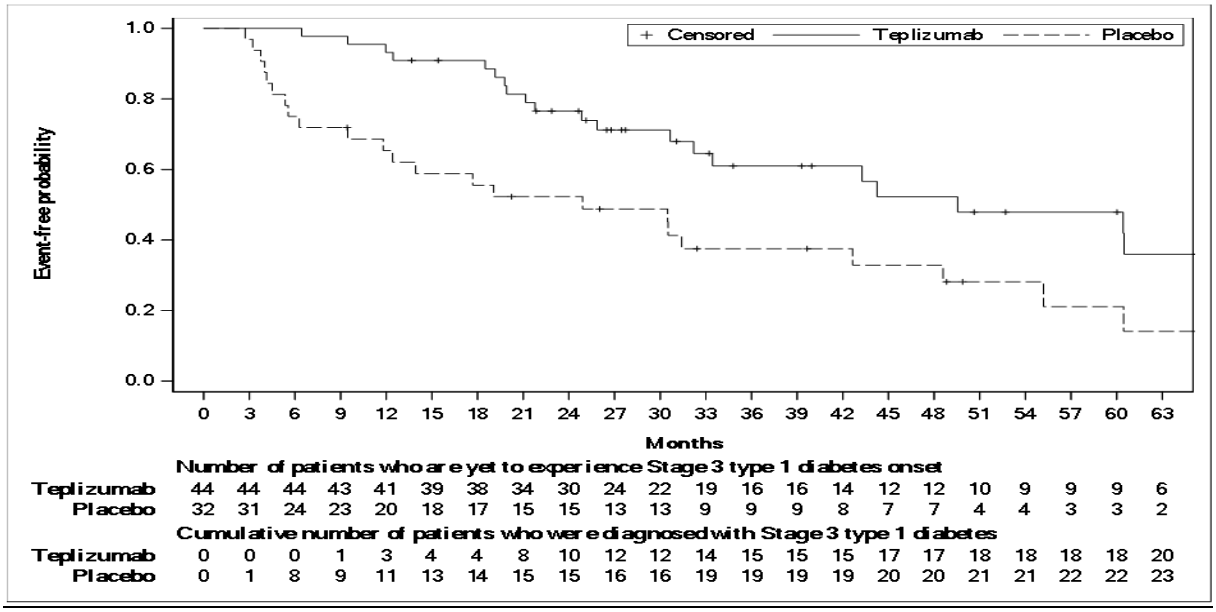
[1] Intent to treat (ITT) population
[2] The glucose data are area under the time-concentration curve (AUC) values from the oral glucose tolerance test.
Abbreviations: HbA1c=haemoglobin A1c, SD=standard deviation, HLA=human leukocyte antigen, GAD65=glutamic acid decarboxylase 65 (GAD) autoantibody, IAA=insulin 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 T1D was diagnosed in 20 (45%) of the patients treated with teplizumab 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, showed that the median time from randomisation to stage 3 T1D diagnosis was 50 months in the teplizumab 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 teplizumab 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]



Number of patients who are yet to experience Stage 3 type 1 diabetes onset																						
Teplizumab	44	44	44	43	41	39	38	34	30	24	22	19	16	16	14	12	12	10	9	9	9	6
Placebo	32	31	24	23	20	18	17	15	15	13	13	9	9	9	8	7	7	4	4	3	3	2
Cumulative number of patients who were diagnosed with Stage 3 type 1 diabetes																						
Teplizumab	0	0	0	1	3	4	4	8	10	12	12	14	15	15	15	17	17	18	18	18	18	20
Placebo	0	1	8	9	11	13	14	15	15	16	16	19	19	19	19	20	20	21	21	22	22	23

[1] ITT population

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Teizeild containing teplizumab in one or more subsets of the paediatric population in prevention of stage 3 type 1 diabetes mellitus as per paediatric investigation plan (PIP) EMEA-000524-PIP02-24, for the granted indication (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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

Absorption

There is no information about absorption since teplizumab 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).

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

Renal impairment
No specific studies to evaluate the pharmacokinetics of teplizumab in patients with renal impairment have been performed.

Hepatic impairment
No specific studies to evaluate the pharmacokinetics of teplizumab in patients with hepatic impairment have been performed.

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

5.3 Preclinical safety data

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. No long-term studies have been performed to assess the carcinogenic potential of teplizumab. Based on the weight of evidence assessment and the proposed long term immunomodulatory mode of action a very low potential carcinogenicity risk cannot fully be excluded.

Developmental and reproductive toxicity

Non-clinical studies conducted in mice using a surrogate antibody directed towards murine CD3 indicate direct or indirect harmful with respect to pregnancy and embryonic/foetal development.

In an embryo-foetal developmental toxicity study in pregnant mice by subcutaneous injection at dose levels of 0, 0.03, 0.3, or 20 mg/kg on gestation days 6, 10, and 14, increase in post-implantation loss occurred in the 20 mg/kg group in the presence of maternal toxicity.

In a pre- and postnatal development toxicity study in pregnant mice 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. Reductions in T cell populations and increases in B cells, and a reduction in the adaptive immune response to keyhole limpet hemocyanin (KLH) were observed in the offspring on postnatal days 35 and 84 at 20 mg/kg. The surrogate antibody was present in the offspring serum at level less than 1.5% that of maternal serum at the high dose. A trend towards reduction in fertility was observed in the offspring of dams at 20 mg/kg.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dibasic sodium phosphate
Monobasic sodium phosphate
Polysorbate 80 (E 433)
Sodium chloride
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. Teizeild should not be infused concomitantly in the same intravenous line with other medicinal products.

Incompatible materials
- Ethylene-propylene copolymer (EPC) and polypropylene (PP) intravenous infusion bags
- Light protected infusion sets
- For Teizeild dose < 68 micrograms: polyethylene (PE) and polyolefin (PO) blend.

This medicinal product should be prepared and administered as instructed in section 4.2 and section 6.6.

6.3 Shelf life

Unopened vial

3 years

After dilution

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

From a microbiological point of view, it is recommended that the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be 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).

From a microbiological point of view, it is recommended that the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 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).

6.4 Special precautions for storage

Store in a refrigerator (2 °C to 8 °C).
Do not freeze.
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.

6.5 Nature and contents of container

Teizeild 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 sizes of 1, 10 or 14 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Preparation for intravenous administration

- Must dilute Teizeild prior to use. This requires a two-step dilution process.
- In preparation for dilution, inspect the vial visually before use (the solution should be clear and colourless). Do not use if particulate matter or colouration is seen.
- Prepare 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).

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), polycarbonate (PC) or glass)

- 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), two (2) Teizeild vials may be needed for days 5 through 14.

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

- Prepare two (2) dilution solutions
- Add the cumulative volume for the calculated dose to a single infusion bag or syringe

- Remove 2 mL of Teizeild 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 (e.g. using the Mosteller formula) before treatment.

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

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

- Calculate the volume of 100 mcg/mL Teizeild solution (prepared in Step 1) to be further diluted in Step 2.

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

Step 2: Final dilution
There are two different methods for intravenous administration of final dilution: infusion bag or syringe pump infusion. Use the appropriate calculation depending on the selected method.

- Infusion bag for intravenous administration:
    - Using an appropriately sized syringe (e.g. 5 mL), withdraw the volume of diluted solution required for that day's calculated dose from the 100 mcg/mL solution (see Step 1: Initial dilution (1:10)).
    - Slowly add contents of the syringe containing the dose to a PVC with DEHP infusion bag containing 25 mL sodium chloride 9 mg/mL (0.9%) 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, PC or glass) for intravenous infusion via syringe pump [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.

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

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

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

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

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

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

    - 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 Teizeild 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). The 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.

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

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

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

Disposal

The unused portion of remaining diluted Teizeild solution in the PVC with DEHP infusion bag, syringe or sterile glass vial should be discarded.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

8. MARKETING AUTHORISATION NUMBERS

EU/1/25/1998/001
EU/1/25/1998/002
EU/1/25/1998/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

AGC Biologics
21511 23rd Drive SE
Bothell, WA 98021
USA

Name and address of the manufacturer responsible for batch release

Sanofi B.V.
Paasheuvelweg 25
1105 BP Amsterdam
Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of Teizeild in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational program, including

communication media, distribution modalities, and any other aspects of the program, with the National Competent Authority.
The educational program is aimed at providing information related to the risks associated with the use of Teizeild and how to manage them.

The MAH shall ensure that in each Member State where Teizeild is marketed, all healthcare professionals (HCPs) and patients/caregivers who are expected to prescribe, dispense, use Teizeild have access to/are provided with the following educational/safety advice tools message to be disseminated through professional bodies:

- Guide for risk minimisation for Healthcare Professionals: Healthcare Professional Guide
- Guide for risk minimisation for Patients: Patient Guide

Healthcare Professional Guide
The objective is to ensure (at prescription and initiation of the treatment with teplizumab) a conversation between the prescribing/treating HCPs and the patient/legal representative around specific information and important recommendation related to the treatment with teplizumab. These are pertaining to the following safety concerns:

- Cytokine release syndrome,
- Lymphopenia,
- Severe infections.

The HCP guide includes the following key elements:

- Information related to the requirement to premedicate patients, to monitor total blood count, liver enzymes prior to, during or after the treatment,
- Guidance for vaccination prior to or after the treatment.

Patient Guide
Objective of this guide is for patients treated with teplizumab and their legal representative to know the risks related to the use of teplizumab and to be able to recognize the signs and symptoms indicative of those risks.

At the time of treatment initiation, the patient guide will be given by the HCPs to the patient/legal representative (which the patient should keep and be able to share with other HCPs involved with their treatment). HCPs can download this patient guide in countries, where available. The patient guide helps the patient identify the following safety concerns:

- Cytokine release syndrome,
- Lymphopenia,
- Severe infections.

The patient guide includes the following key elements:

- Information to educate patient about signs/symptoms which could be indicative of these risks and to tell their doctor or nurse immediately if these occur,
- Guidance for vaccinations prior to or after the treatment,
- Recommendation for the patients/legal representative to read the package leaflet (PL) thoroughly.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Teizeild 1 mg/mL concentrate for solution for infusion
teplizumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each vial contains 2 mg of teplizumab in 2 mL of concentrate.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, polysorbate 80 (E 433), sodium chloride, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion

1 vial, 2 mg/2 mL
10 vials, 2 mg/2 mL
14 vials, 2 mg/2 mL

5. METHOD AND ROUTE OF ADMINISTRATION

For single use only.
Intravenous use after dilution.
Read the package leaflet before use.
[QR code to be included]
teizeild.info.sanofi

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Read the leaflet for the shelf life after dilution.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.
Store upright.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

12. MARKETING AUTHORISATION NUMBERS

EU/1/25/1998/001 1 vial
EU/1/25/1998/002 10 vials
EU/1/25/1998/003 14 vials

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTES OF ADMINISTRATION

Teizeild 1 mg/mL sterile concentrate
teplizumab
IV after dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 mg/2 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Teizeild 1 mg/mL concentrate for solution for infusion
teplizumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, nurse or pharmacist.
- If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Teizeild is and what it is used for
2. What you need to know before you are given Teizeild
3. How Teizeild is given
4. Possible side effects
5. How to store Teizeild
6. Contents of the pack and other information

1. What Teizeild is and what it is used for

Teizeild is a medicine that contains the active substance teplizumab. Teplizumab is a monoclonal antibody, a type of protein designed to recognise and attach to a target.

Teizeild is used in adults and children 8 years of age and older who have stage 2 type 1 diabetes (T1D). It is used to delay the onset of stage 3 T1D in these patients.

Type 1 diabetes (T1D) is an autoimmune condition that occurs when your own immune system (the body's natural defences) mistakenly attacks cells in the pancreas (called beta cells) that make insulin (a hormone that controls the amount of glucose (sugar) in the blood). Over time, this leads to a complete lack of insulin in the body.

T1D develops in three stages. In stage 1 T1D, your blood sugar levels are normal and you don't have any symptoms. In stage 2 T1D, your blood sugar levels start to increase and become abnormal. In stage 3 T1D, your body cannot make enough insulin on its own to control your blood sugar and you need insulin treatment to manage the condition.

Before starting treatment with Teizeild your doctor will confirm that you have stage 2 T1D by ensuring that you test positive for 2 or more autoantibodies (a type of protein made by the immune system indicating the autoimmune destruction of beta cells in the pancreas) and have dysglycaemia without persistently high blood sugar levels (overt hyperglycaemia).

The active substance in Teizeild, teplizumab, binds to an activating molecule on the surface of T cells (a type of white blood cell) known as CD3. By binding to CD3, teplizumab deactivates the T cells that attack and destroy beta cells which helps to preserve beta cell function and slows down the progression of T1D.

If you have any questions on how Teizeild works or about your treatment with Teizeild, ask your doctor, nurse or pharmacist.

2. What you need to know before you are given Teizeild

You must not be given Teizeild
- if you are allergic to teplizumab or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, nurse or pharmacist about all your medical conditions before you are given Teizeild, including if you:
- have a serious infection – or an infection that does not go away or that keeps coming back.
- have recently had or are planning to have a vaccine. Teizeild may affect how well a vaccine works. Tell your doctor, nurse or pharmacist that you are being treated with Teizeild before having a vaccine. Depending on the type of vaccine, your doctor will tell you when you can safely receive any vaccine prior to and after the treatment with Teizeild.

After you have been given Teizeild
Tell your doctor or nurse immediately if you have any of the following:
- Fever, nausea, tiredness, headache, muscle pain (myalgia), joint pain (arthralgia) or increased liver enzymes in your blood, which may be signs and symptoms of a serious condition known as cytokine release syndrome (see section 4 “Possible side effects”).
- Fever, chills, tiredness, nausea, vomiting, cough, shortness of breath, chest pain, swollen lymph nodes or a painful, swollen lump that feels warm (abscess). These may be symptoms of an infection (see section 4 “Possible side effects”).
- Hives, rash, joint pain or swelling, itching, dizziness, wheezing, difficulty breathing or swelling of your tongue and lips. These may be symptoms of allergic reactions (see section 4 “Possible side effects”).

Teizeild may lower your lymphocyte count, a type of white blood cells that helps fight infections (see section 4 “Possible side effects”).

Your doctor will do blood tests to check your liver and your complete blood counts before you start treatment and during treatment with Teizeild.

Patient Guide
Your doctor will provide you with a patient guide that includes information about possible side effects, their symptoms, and instructions on what to do if they occur. Read it carefully and ask your doctor if you have any questions about your treatment.

Children
The safety and efficacy of Teizeild in children under 8 years of age have not been established.

Other medicines and Teizeild
Tell your doctor, nurse or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding
Tell your doctor, nurse or pharmacist if you are pregnant, think you may be pregnant or are planning to have a baby. Teizeild may harm your unborn baby.
- Teizeild is not recommended during pregnancy and in women who can have children who are not using contraception (birth control).

Tell your doctor, nurse or pharmacist if you are breast-feeding or are planning to breast-feed. It is not known if Teizeild passes into your breast milk and if it can harm your baby.

- It is recommended to stop breast-feeding during treatment with Teizeild and for 30 days after the last dose.

Driving and using machines
Teizeild has minor effects on your ability to drive and use machines. If you feel tired (fatigue) (see section 4 "Possible side effects"), do not drive or use machines before discussing it with your doctor, nurse or pharmacist.

Teizeild contains sodium and polysorbate 80
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

This medicine contains 0.10 mg of polysorbate 80 in each vial which is equivalent to 0.05 mg/mL. Polysorbates may cause allergic reactions. Tell your doctor if you or your child have any known allergies.

3. How Teizeild is given

Teizeild should be given to you by a healthcare professional with access to appropriate medical support needed to manage serious side effects. Teizeild is given as an infusion (drip) into a vein (intravenous (IV)).

Your doctor will determine your dose of Teizeild based on your body surface area, which is a way of measuring the total area of your skin.

How often Teizeild is given
You will be given the infusion once a day for 14 days. Each infusion will last a minimum of 30 minutes.

For the first 5 days of treatment, your doctor or nurse will give you other medicines by mouth to reduce your risk of developing cytokine release syndrome.

These medicines include:
- ibuprofen or naproxen – or other medicines for fever such as paracetamol
- an antihistamine – a medicine used to treat allergies
- an anti-nausea medicine.

If you are given more Teizeild than you should
If you are given too much Teizeild, your doctor will treat and monitor any side effects you may have.

If you miss a Teizeild infusion
If you miss a scheduled infusion, your doctor or nurse will continue your treatment on the next scheduled day. You will not get 2 infusions on the same day.

If you have any further questions on the use of this medicine, ask your doctor, nurse or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

During and after your treatment with Teizeild, your doctor or nurse will check for serious side effects, as well as other side effects, and treat you as needed.

Serious side effects
Tell your doctor or nurse immediately if you have any of the following serious side effects:

Very common (may affect more than 1 in 10 people)
Decrease in lymphocytes (a type of white blood cells), as measured in blood tests.

- This can happen after your first dose.
- This can affect how well your body can fight infections.
- Longer and more severe decreases in lymphocytes could make you more susceptible to infections (see section 2 "What you need to know before you are given Teizeild").
- Your lymphocytes counts should start to go back to normal after your fifth dose of Teizeild.

Common (may affect up to 1 in 10 people)
Cytokine release syndrome (CRS)
The signs and symptoms may start during the first 5 days of treatment and may include:

- fever
- feeling tired
- muscle and joint pain
- nausea
- headache
- increased liver enzymes and bilirubin (a breakdown product of red blood cells) in your blood.

Uncommon (may affect up to 1 in 100 people)
- Infections, with symptoms such as fever, chills, tiredness, nausea, vomiting, cough, shortness of breath, chest pain, swollen lymph nodes or a painful, swollen lump that feels warm (abscess)
- Hypersensitivity, with symptoms such as hives, rash, joint pain or swelling, itching, dizziness, wheezing, difficulty breathing or swelling of your tongue and lips.

Other side effects
Tell your doctor or nurse if you have any of the following side effects:

Very common (may affect more than 1 in 10 people)
- Low levels of blood platelets, components that help the blood to clot (thrombocytopenia)
- Low levels of neutrophils, a type of white blood cell (neutropenia)
- Low levels of white blood cells (leucopenia)
- Decrease in haemoglobin (the protein in red blood cells that carries oxygen around the body)
- Headache
- Vomiting
- Nausea
- Increase in liver enzyme levels
- Rash
- Itching (pruritus)
- Fever (pyrexia)
- Feeling tired (fatigue)

Common (may affect up to 1 in 10 people)
- Increased levels of eosinophils, a type of white blood cell (eosinophilia)
- Diarrhoea
- Abdominal (belly) pain
- Increase in bilirubin levels
- Itchy skin

- Red and itchy raised bumps (hives)
- Skin exfoliation
- Chills

Not known (frequency cannot be estimated from the available data)
- Mononucleosis (Epstein-Barr virus) reactivation
- Pain
- Illness

Your doctor or nurse may pause or stop your treatment if you get liver problems, have a serious infection, or if your blood counts stay too low.

Reporting of side effects
If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Teizeild

Your doctor, pharmacist or nurse is responsible for storing this medicine and disposing of any unused product correctly. The following information is intended for healthcare professionals.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the vial after "EXP". The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C to 8 °C). Do not freeze the vials.
Keep the vial in the outer carton in order to protect from light.
Store upright.

After dilution

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

From a microbiological point of view, it is recommended that the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be 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).

From a microbiological point of view, it is recommended that the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 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).

Do not throw away medicines via wastewater or household waste. Ask your doctor or nurse how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Teizeild contains
- The active substance is teplizumab
- One vial contains 2 mg of teplizumab
- The other ingredients (excipients) are dibasic sodium phosphate, monobasic sodium phosphate, polysorbate 80 (E 433), sodium chloride, and water for injections (see section 2 “Teizeild contains sodium and polysorbate 80”).

What Teizeild looks like and contents of the pack
Teizeild is a concentrate for solution for infusion in a vial (1 mg/mL). It is a clear, colourless solution. Teizeild is supplied in a carton pack containing 1, 10 or 14 vials.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

Manufacturer
Sanofi B.V.
Paasheuvelweg 25
1105 BP Amsterdam
Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Preparation for intravenous administration

- Must dilute Teizeild prior to use. This requires a two-step dilution process.

- In preparation for dilution, inspect the vial visually before use (the solution should be clear and colourless). Do not use if particulate matter or colouration is seen.
- Prepare 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 package leaflet, section "How to store Teizeild").

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), polycarbonate (PC) or glass)

- Remove the cap from the vial – this is the preparation start time.

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

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

- Prepare two (2) dilution solutions
- Add the cumulative volume for the calculated dose to a single infusion bag or syringe

- Remove 2 mL of Teizeild 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 (e.g. using the Mosteller formula) before treatment.

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

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

- Calculate the volume of 100 mcg/mL Teizeild solution (prepared in Step 1) to be further diluted in Step 2.

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

Step 2: Final dilution
There are two different methods for intravenous administration of final dilution: infusion bag or syringe pump infusion. Use the appropriate calculation depending on the selected method.

- Infusion bag for intravenous administration:

    - Using an appropriately sized syringe (e.g. 5 mL), withdraw the volume of diluted solution required for that day's calculated dose from the 100 mcg/mL solution (see Step 1: Initial dilution (1:10)).
    - Slowly add contents of the syringe containing the dose to a PVC with DEHP infusion bag containing 25 mL sodium chloride 9 mg/mL (0.9%) 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, PC or glass) for intravenous infusion via syringe pump [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.

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

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

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

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

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

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

    - 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 Teizeild 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). The 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.

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

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

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

Disposal

The unused portion of remaining diluted Teizeild solution in the PVC with DEHP infusion bag, syringe or sterile glass vial should be discarded.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.