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

TEPEZZA 500 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 500 mg of teprotumumab. Teprotumumab is a fully human IgG1 monoclonal antibody produced in Chinese Hamster Ovary cells by recombinant DNA technology.

The reconstituted solution contains 47.6 mg/mL (500 mg / 10.5 mL) of teprotumumab.

Excipient with known effect

This medicinal product contains 1.05 mg of polysorbate 20 in each 10.5 mL reconstituted volume.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion (powder for concentrate)

White to off-white lyophilised powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TEPEZZA is indicated in adults for the treatment of moderate to severe thyroid eye disease (TED).

4.2 Posology and method of administration

Treatment with this medicinal product must be initiated and supervised by a physician experienced in the diagnosis and treatment of thyroid eye disease. It should be administered by a healthcare professional and under the supervision of a physician with access to appropriate medical support to manage infusion-related reactions.

Posology

Dosing is based on the patient's actual body weight. The recommended dose is 10 mg/kg of body weight for the initial dose followed by 20 mg/kg of body weight for 7 additional doses given once every three weeks as an intravenous infusion.

For the first 2 infusions, the diluted solution is administered as an intravenous infusion over at least 90 minutes. If well tolerated, infusions 3 to 8 can be administered over 60 minutes every three weeks (see Method of administration). Clinical response is expected with 8 doses of treatment. Additional doses should not be administered if response is not achieved with this regimen.

Recommended pre-medication

For patients experiencing immediate hypersensitivity reactions or infusion-related reactions during the first two infusions of teprotumumab, pre-medication with an antihistamine, antipyretic, corticosteroid products and/or administering all subsequent infusions at a slower infusion rate is recommended (see section 4.4).

Special populations

Elderly
No dose adjustment is considered necessary in patients over 65 years old (see section 5.2).

Renal impairment
Renal impairment is generally not expected to have any significant impact on the pharmacokinetics of monoclonal antibodies. Therefore, no dose adjustment is considered necessary for patients with renal impairment (see section 5.2).

Hepatic impairment
Hepatic impairment is generally not expected to have any significant impact on the pharmacokinetics of monoclonal antibodies. Therefore, no dose adjustment is considered necessary for patients with hepatic impairment (see section 5.2).

Paediatric population
Teprotumumab should not be used in children from birth to adolescence before growth is complete because of safety concerns related to potential decrease in bone mass and decrease in body weight gains (see section 5.3).

The safety and efficacy of teprotumumab in adolescents whose growth is complete to less than 18 years has not been established. No data are available.

Method of administration

- This medicinal product must be administered as an intravenous infusion. It must not be administered as an intravenous push or bolus.
- Prior to infusion:
  - the powder must be reconstituted with water for injection.
  - The reconstituted solution must be further diluted in sodium chloride 9 mg/mL (0.9%) solution for infusion.
- TEPEZZA must not be co-administered with other medicinal products through the same infusion line.
- For the first 2 infusions, the diluted solution must be administered intravenously over at least 90 minutes. If well tolerated, the minimum time for subsequent infusions can be reduced to 60 minutes.
- If the 60-minute infusion is not well tolerated, the minimum time for subsequent infusions should remain at 90 minutes, the rate of infusion should be reduced and pre-medication is recommended for subsequent infusions.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Infusion-related reactions

Teprotumumab may cause infusion reactions. Infusion reactions have been reported in approximately 4% of patients treated with teprotumumab (see section 4.8).

Infusion reactions may occur during any of the infusions or within 90 minutes after an infusion. Patients should be monitored closely throughout the infusion and for 90 minutes after completion of infusion.

Following the monitoring period, patients should be advised to contact their healthcare professionals if symptoms of infusion-related reactions, including transient hypertension, feeling hot, tachycardia, dyspnoea, headache, abdominal pain, muscular pain, palpitations, rash, haptic hallucinations, sleep paralysis, nasal congestion, urticaria, or diarrhoea occur.

Based on the severity of the infusion-related reaction, infusion should be interrupted or discontinued, and appropriate medical management should be instituted. In patients who experience an infusion reaction, consideration should be given to pre-medicating with an antihistamine, antipyretic, corticosteroid and/or administering all subsequent infusions at a slower infusion rate.

Hearing impairment

Teprotumumab may cause severe hearing impairment including hearing loss, which in some cases may be permanent. Events associated with hearing impairment including hearing loss (reported as deafness, neurosensory hypoacusis, deafness unilateral, eustachian tube dysfunction, eustachian tube patulous, hyperacusis, hypoacusis, autophony and tinnitus and tympanic membrane disorder) have been observed in clinical trials (13.8%) and post-marketing experience with teprotumumab (see section 4.8).

Patients should be advised to report symptoms of altered hearing promptly to their healthcare professional.

For patients with pre-existing hearing impairment, worsening of hearing impairment symptoms during or after the completion of the treatment with teprotumumab can occur. The benefit-risk of treatment should be considered in these patients.

Patient's hearing should be assessed using audiometry before starting treatment (first infusion), during treatment (around the third or fourth infusion) and after completing treatment with teprotumumab. If a patient experiences subjective hearing changes during treatment, additional audiometric assessments are recommended, as necessary. It is advised to monitor for hearing changes in all patients for 6 months after completion of treatment. Prolonged follow-up may be needed for patients who develop hearing changes, at the discretion of the treating physician.

It should be strongly considered to discontinue teprotumumab in patients experiencing hearing loss that requires intervention, limits their ability to self-care, or is considered profound.

Concomitant therapies

Caution is needed when co-administering teprotumumab in patients who are receiving concomitant therapies known to cause ototoxicity (e.g. aminoglycosides, vancomycin, platinum containing

chemotherapeutic medicinal products, loop diuretics) due to the potential risk of additive effects on hearing impairment.

No interaction has been identified between teprotumumab and medicinal products that are known to cause muscle spasms (e.g. anti-thyroid drugs, fluoroquinolones, statins) (see section 4.5).

Hyperglycaemia

Hyperglycaemia may occur in patients treated with teprotumumab. Events associated with hyperglycaemia include blood glucose increased, diabetes mellitus, glucose tolerance impaired and glycosylated haemoglobin increased. In double-blind TED clinical trials, 13.2% of patients (80% of whom had pre-existing pre-diabetes or pre-existing diabetes mellitus) experienced hyperglycaemia or events associated with hyperglycaemia. One patient developed diabetic ketoacidosis. In the post-marketing setting, cases of hyperosmolar hyperglycaemic state have also been observed in patients with pre-diabetes and diabetes (see section 4.8).

Hyperglycaemia and related events should be managed with medicinal products for glycaemic control, if necessary. Patients must be assessed for elevated blood glucose and symptoms of hyperglycaemia prior to infusion and must be monitored while on treatment with teprotumumab. Patients with hyperglycaemia or pre-existing diabetes must be under appropriate glycaemic control before and while receiving teprotumumab (see section 4.8). Blood glucose monitoring is recommended for 6 months after completion of treatment with teprotumumab.

Exacerbation of pre-existing inflammatory bowel disease (IBD)

Teprotumumab may cause an exacerbation of pre-existing inflammatory bowel disease (IBD). Patients with IBD should be monitored for flare of disease. If IBD exacerbation is suspected, discontinuation of treatment should be considered. Patients with pre-existing inflammatory bowel disease were excluded from clinical studies (see section 4.8).

Contraception

Women of childbearing potential should use effective contraception during and for at least 6 months, after the last administration of teprotumumab (see section 4.6).

Additional precautions for use

Patients should be advised to stop smoking and avoid high intensity noises during treatment with teprotumumab. Additionally, blood pressure should be appropriately controlled before and while receiving teprotumumab.

Educational materials

All physicians who intend to prescribe TEPEZZA must ensure that they have received and are familiar with the healthcare professional educational material. Physicians must discuss the benefits and risks of this medicinal product with the patient and provide them with the patient guide. Patients should be instructed to seek immediate medical attention if they experience any signs or symptoms of hearing impairment during therapy. Women of childbearing potential must use effective contraception during treatment and should contact their treating physician immediately if they become pregnant.

Excipient with known effect

This medicinal product contains 1.05 mg of polysorbate 20 in each 10.5 mL reconstituted volume. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Since teprotumumab is cleared from the circulation by proteolytic catabolism, no metabolic interactions with other medicinal products are expected.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception

Women of childbearing potential should use effective contraception (methods that result in less than 1% pregnancy rates) prior to initiation, during treatment and for 6 months after the last administration of teprotumumab.

Pregnancy

There are no adequate data from the use of teprotumumab in pregnant women.

Studies in animals have shown developmental toxicity (see section 5.3).

Based on the mechanism of action inhibiting insulin like growth factor-1 receptor (IGF-1R) and the teratogenic effects observed in animal developmental studies, teprotumumab may cause congenital malformations such as foetal growth retardation and developmental anomalies when administered during pregnancy (see section 5.3). Therefore, TEPEZZA is contraindicated during pregnancy (see section 4.3).

If a patient becomes pregnant while taking TEPEZZA, therapy should be discontinued, and the patient advised of the potential risk to the foetus.

Breast-feeding

It is unknown whether teprotumumab is excreted in human milk. Teprotumumab induced developmental toxicity in animals (see section 5.3). Thus, as a precautionary measure, teprotumumab should not be used during breast-feeding.

Fertility

Studies to evaluate the effect of teprotumumab on fertility in humans have not been performed. Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3). Among female participants of childbearing potential, menstrual disorders (Amenorrhea, Dysmenorrhoea, Heavy menstrual bleeding, Hypomenorrhoea, Menstruation irregular) have been reported during clinical trials (see section 4.8).

4.7 Effects on ability to drive and use machines

TEPEZZA has a minor influence on the ability to drive and use machines. Fatigue and headaches have been reported with the use of teprotumumab (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions are muscle spasms (27.6%), diarrhoea (14.5%), alopecia (13.2%), hyperglycaemia (13.2%), fatigue (12.5%), nausea (10.5%) and headache (10.5%).

The most important serious adverse reactions that have been reported are diabetic ketoacidosis (0.7%), conductive deafness (0.7%), deafness (1.3%), deafness unilateral (0.7%),diarrhoea (0.7%), infusion-related reaction (0.7%), diabetes mellitus (2.6%), and inflammatory bowel disease (0.7%), (see section 4.4).

Tabulated list of adverse reactions

Adverse reactions reported in clinical trials and derived from spontaneous reporting are listed below in table 1. The frequencies of adverse reactions are based on 4 placebo-controlled studies with 285 patients (teprotumumab = 152 patients; placebo = 133 patients). Patients were exposed to teprotumumab for a median of 148 days. The adverse reaction frequencies from clinical trials are based on all-cause adverse event frequencies, where a proportion of the events for an adverse reaction may have other causes than the medicinal product, such as the disease, other treatments or unrelated causes.

The adverse reactions are listed by MedDRA System Organ Class and by frequency. Frequencies are defined according to the following convention: 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

MedDRA system organ class	**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)**	**Not known/cannot be estimated from available data**
Infections and infestations		COVID-19			
Metabolism and nutrition disorders		Diabetes mellitus[1], Hyperglycaemia[1], Blood glucose increased[1], Glycosylated haemoglobin increased[1], Glucose tolerance impaired[1]	Diabetic ketoacidosis[1]		Hyperosmolar hyperglycaemic state[1,2]
Nervous system disorders	Headache	Dysgeusia			
Ear and labyrinth disorders		Deafness, Hypoacusis, Neurosensory hypoacusis, Autophony, Eustachian tube dysfunction, Eustachian tube patulous, Ear discomfort, Tinnitus	Conductive deafness, Deafness unilateral, Hyperacusis, Tympanic membrane disorder		
Gastrointestinal disorders	Diarrhoea, Nausea		Inflammatory bowel disease[1]		

MedDRA system organ class	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)	Not known/cannot be estimated from available data
Skin and subcutaneous tissue disorders	Alopecia	Dry skin, Nail bed disorder, Nail discoloration, Onychoclasis, Madarosis	Ingrowing nail		
Musculoskeletal and connective tissue disorders	Muscle spasms				
Reproductive system and breast disorders		Amenorrhea, Hypomenorrhea, Dysmenorrhea, Menstruation irregular, Heavy menstrual bleeding			
General disorders and administration site conditions	Fatigue				
Investigations		Weight decreased			
Injury, poisoning and procedural complications		Infusion-related reaction[1]			

[1] See below description of selected adverse reactions
[2] Observed in the post-marketing setting – frequency cannot be estimated from the available data

Description of selected adverse reactions

Infusion-related reactions
Infusion-related reactions were observed in 3.9% patients treated with teprotumumab and all were mild or moderate in intensity and transient and were successfully managed with antihistamines and/or corticosteroids, if needed. See sections 4.2 and 4.4 for action to be taken in case of infusion-related reactions.

Hearing impairment
In clinical studies, hearing impairment includes hearing loss [hypoacusis (5.3%), tinnitus (3.3%), deafness (1.3%), neurosensory hypoacusis (1.3%) and deafness unilateral (0.7%), eustachian tube dysfunction (1.3%), eustachian tube patulous (1.3%), autophony (1.3%), hyperacusis (0.7%) and tympanic membrane disorder (0.7%)]. One patient (0.7%) with pre-existing hearing impairment reported an event of neurosensory hypoacusis, which led to the discontinuation of teprotumumab. Additionally, one patient (0.7%) with pre-existing hearing impairment reported a serious event of conductive deafness, also resulting in the discontinuation of teprotumumab. For clinical management of hearing impairment, see section 4.4.

Hyperglycaemia
In clinical studies, hyperglycaemia (5.3%) and events associated with hyperglycaemia including blood glucose increased (3.3%), diabetes mellitus (2.6%), glucose tolerance impaired (1.3%), glycosylated haemoglobin increased (2.0%) were mild or moderate in severity and managed as needed with treatments used for glycaemic control. One event of diabetic ketoacidosis (0.7%) was reported in clinical studies for a patient who received a single-dose of teprotumumab. Post-marketing cases of hyperosmolar hyperglycaemic state have been reported. The events of diabetes mellitus, diabetic ketoacidosis, and hyperosmolar hyperglycaemic state all occurred in patients with pre-existing

diabetes or pre-existing pre-diabetes, and other co-morbidities. Patients with diabetes or pre-diabetes at baseline may experience increased hyperglycaemic excursion, as insulin and IGF-1 receptors are homologous and share downstream signalling pathways. Recommendations for management of hyperglycaemia are provided in section 4.4.

Inflammatory bowel disease (IBD)
In study TED01RV, a teprotumumab-treated participant, who had a pre-existing IBD, experienced severe diarrhoea. This serious adverse reaction (0.7%) led to the discontinuation of treatment, see section 4.4.

Alopecia and madarosis
In clinical studies, 13.2% of patients treated with teprotumumab experienced alopecia, and 2.0% experienced madarosis. Most cases were mild. Patients may experience unresolved hair loss after completing teprotumumab treatment.

Muscle spasms
In clinical studies, muscle spasms were the most commonly reported adverse events, occurring in 27.6% of patients. Some of these events developed greater than 4 months after the last infusion and lasted for more than 3 months. The majority of the events were mild, transient, self-limiting and were manageable without the need for interruption of teprotumumab treatment.

Onychoclasis
In clinical studies, onychoclasis was reported in 2.0% of patients and some of these events lasted for more than 3 months.

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 known antidote for teprotumumab overdose. Treatment consists of discontinuation of the medicinal product and supportive therapy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, monoclonal antibodies, ATC code: L04AG13

Mechanism of action

Teprotumumab mechanism of action in patients with TED has not been fully characterised. Teprotumumab binds to IGF-1R and blocks its activation and signalling.

Clinical efficacy and safety

The efficacy and safety of teprotumumab was assessed in 287 patients with thyroid eye disease in four randomised, double-blind, placebo-controlled clinical studies (TED01RV, OPTIC, OPTIC-J and HZNP-TEP-403).

In all studies, patients received teprotumumab administered as an initial 10 mg/kg intravenous infusion followed by 20 mg/kg infusions every 3 weeks for a total of 8 infusions.

Patients were to be euthyroid or had thyroxine and free triiodothyronine levels less than 50% above or below normal limits. Patients with optic neuropathy were excluded.

Patients who had received immunosuppressive therapies (including rituximab, tocilizumab, or any other non-steroidal immunosuppressive agent within 3 months prior to screening), as well as those who had used oral or intravenous steroids within 4 weeks prior to screening, were not permitted in the studies. Additionally, patients who had undergone orbital irradiation or any surgical treatment for thyroid eye disease were also excluded.

Active thyroid eye disease

Studies TED01RV, OPTIC, and OPTIC-J enrolled 225 patients 18 years and older with active thyroid eye disease (111 randomised to teprotumumab, and 114 to placebo).

Patients with active thyroid eye disease had a mean time since diagnosis of TED of 5.74 months, mean proptosis for the study eye of 22.52 mm, and mean clinical activity score CAS for the study eye of 5.0.

The baseline demographic and disease characteristics of the study population of TED01RV, OPTIC and OPTIC-J studies were: median age 52.0 years (range: 20 to 79); 14.2% patients 65 years or older; 72.4% female; 76.0% non-smoker.

The primary endpoint in phase II study TED01RV was the overall responder rate, defined as the percentage of participants with ≥ 2-point reduction in CAS and ≥ 2 mm reduction in proptosis measurement from baseline in the study eye, provided there is no corresponding deterioration (≥ 2-point increase in CAS or ≥ 2 mm increase in proptosis in the fellow eye) at week 24.

Efficacy results of study TED01RV are summarised in table 2.

Table 2. Overview of efficacy parameters in study TED01RV at week 24 (ITT population)

	Teprotumumab (N = 42)	**Placebo (N = 45)**	**Treatment Difference (95% CI)**	**p-value**
Primary endpoint				
Overall responder rate, %	69.0	20.0	48.9 (30.2, 67.6)	< 0.001[a]
Secondary endpoints[b]				
Proptosis in study(mm), LS Mean	-2.95	-0.30	-2.65 (-3.38, -1.92)	< 0.001
CAS in study eye, LS Mean	-4.04	-2.49	-1.55 (-2.17, -0.94)	< 0.001
Change from baseline in GO-QoL visual functioning, LS Mean	24.31	9.70	14.61 (4.37, 24.84)	0.006

CAS = Clinical Activity Score; CI = confidence interval; ITT = intent-to-treat; GO-QoL = Graves' Ophthalmopathy Quality of Life; LS = Least Squares

Note: Results shown are those for the study eye for overall responder rate and change from baseline in proptosis.

[a] P-value was obtained from a logistic regression model with treatment and smoking status as covariate. Odds ratio of teprotumumab over placebo was 8.86 (95% CI [3.29, 23.83]).

[b] For secondary endpoints, analysis results were obtained from a mixed model for repeated measures (MMRM) with an unstructured covariance matrix using treatment, smoking status, baseline value, visit, treatment by visit, and visit by baseline value interaction as fixed effects. A change from baseline of zero was imputed at the first baseline visit for patients with no post-baseline assessment.

Note: For GO-QoL analysis variables, a transformed score is the sum of scores from individual questions to a scale of 0 (worst health) to 100 (best health).

After 48-weeks off-treatment, 14 of 29 proptosis responders (48.3%) in the teprotumumab group maintained responder status, and 11 of 29 (37.9%) experienced a relapse. Relapse was defined as increase in proptosis of ≥ 2 mm from week 24 in the study eye.

The primary endpoint, in the phase III OPTIC and the OPTIC-J studies was the proptosis responder rate at week 24 (defined as the proportion of patients with a ≥ 2 mm reduction in proptosis from baseline in the study eye, without deterioration (≥ 2 mm increase) in proptosis in the fellow eye).

Efficacy results of the OPTIC and OPTIC-J studies are summarised in tables 3 and 4, respectively.

Table 3. Overview of efficacy parameters in study OPTIC at week 24 (ITT population)

	Teprotumumab (N = 41)	**Placebo (N = 42)**	**Treatment Difference (95% CI)**	**p-value**
Primary endpoint				
Proptosis responder rate, %	82.9	9.5	73.5 (58.9, 88.0)	< 0.001[a]
Secondary endpoints				
Overall responder rate, %	78.0	7.1	70.8 (55.9, 85.8)	< 0.001[a]
CAS responder rate, %	58.5	21.4	36.0 (17.4, 54.7)	< 0.001[a]
Change from baseline in proptosis (mm) through week 24, LS mean	-2.82	-0.54	-2.28 (-2.77, -1.80)	< 0.001[b]
Diplopia responder rate, %[c]	67.9	28.6	39.3 (15.6, 63.0)	< 0.001[a]
Change from baseline in GO-QoL visual functioning, LS mean	15.40	2.86	12.54 (3.14, 21.94)	0.010[b]
Change from baseline in GO-QoL appearance, LS mean	18.84	0.37	18.47 (9.95, 27.00)	< 0.001[b]

CAS = Clinical Activity Score; CI = confidence interval; GO-QoL = Graves' Ophthalmopathy Quality of Life; ITT = intent-to-treat; LS = Least Squares

Note: Results shown are those for the study eye for proptosis responder rate, overall responder rate, CAS responder rate, and diplopia responder rate.

Overall responder rate = Overall responders are defined as achieving ≥ 2 points reduction in CAS and ≥ 2 mm reduction in proptosis from baseline, provided there was no corresponding deterioration (≥ 2 points/mm increase) in CAS or proptosis in the fellow eye at week 24.

CAS responder rate = CAS responders are defined as achieving a reduction to a CAS of 0 or 1 at week 24.

Diplopia responder rate = Diplopia responders are defined as achieving ≥ 1 grade reduction in diplopia in the study eye without worsening by at least one grade in the fellow eye at week 24.

[a] Cochran–Mantel–Haenszel (CMH) test stratified by tobacco use status (smoker vs non-smoker).

[b] Results obtained from mixed model repeated measurements (MMRM) analysis with an unstructured covariance matrix including baseline value, tobacco use status, treatment group, visit, visit by treatment, and visit by baseline value interactions. A change from baseline of 0 was imputed at the first post baseline visit for any patient without a post-baseline value at all.

[c] Evaluated based on only those who presented diplopia at baseline.

Of 34 proptosis responders at week 24, 10 (29.4%) relapsed during the 48-week off-treatment follow-up. Among the 21 who had assessments at week 72, 19 (90.5%) maintained their responder status.

Table 4. Overview of efficacy parameters in study OPTIC-J at week 24 (ITT population)

	Teprotumumab (N = 27)	Placebo (N = 27)	Treatment Difference (95% CI)	p-value
Primary endpoint				
Proptosis responder rate, %	88.9	11.1	77.8 (60.7, 94.8)	< 0.0001[a]
Secondary endpoints				
Overall responder rate, %	77.8	3.7	74.1 (56.9, 91.3)	< 0.0001[a]
CAS responder rate, %	59.3	22.2	37.0 (12.5, 61.6)	0.0031[a]
Change from baseline in proptosis, LS mean	-2.36	-0.37	-1.99 (-2.75, -1.22)	< 0.0001[b]

CAS = Clinical Activity Score; CI = confidence interval; ITT = intent-to-treat; LS = least squares
Note: Results shown are those for the study eye, for proptosis responder rate, overall responder rate, and CAS responder rate.
Overall responder rate = Overall responders are defined as achieving ≥ 2 points reduction in CAS and ≥ 2 mm reduction in proptosis from baseline, provided there was no corresponding deterioration (≥ 2 points/mm increase) in CAS or proptosis in the fellow eye at week 24.
CAS responder rate = CAS responders are defined as achieving a reduction to a CAS of 0 or 1 at week 24.
[a] p-value was estimated from Cochran-Mantel-Haenszel test adjusted for the randomisation stratification factor (tobacco use status).
[b] p-value is from mixed model repeated measurements analysis with an unstructured variance-covariance matrix including change from baseline value as the dependent variable and the following covariates: Baseline value, treatment group, tobacco use status, visit, visit-by-treatment and visit-by-baseline value interactions.

Chronic thyroid eye disease

Phase IV study (HZNP-TEP-403) enrolled 62 patients with chronic thyroid eye disease (42 randomised to teprotumumab and 20 to placebo). Patients with chronic thyroid eye disease had a mean time since diagnosis of TED of 5.18 years, mean proptosis for the study eye of 24.40 mm, and mean CAS for the study eye of 0.4. The baseline demographic and disease characteristics of the study population were: median age 49 years (range: 18 to 75); 85.5% patients under 65 years, 14.5% patients 65 years or older; 80.6% female, and 87.1% non-smokers.

The primary endpoint in study HZNP-TEP-403 was the mean change from baseline in proptosis at week 24 in the study eye. The first secondary endpoint was the proptosis responder rate defined as the percentage of participants with a ≥ 2 mm reduction from baseline in proptosis in the study eye, without deterioration (≥ 2 mm increase) of proptosis in the fellow eye at week 24.

Efficacy results of HZNP-TEP-403 are summarised in table 5.

Table 5. Overview of efficacy parameters in study HZNP-TEP-403 at week 24 (intent-to-treat population)

	Teprotumumab (N = 42)	Placebo (N = 20)	Treatment Difference (95% CI)	p-value
Primary endpoint				
Change from baseline in proptosis at week 24, LS mean	-2.41	-0.92	-1.48 (-2.28, -0.69)	0.0004[a]
Secondary endpoint				
Proptosis responder rate, %	61.9	25.0	36.9 (5.4, 59.2)	0.0134[b]
Change from baseline in GO-QoL visual functioning, LS mean	8.73	2.41	6.31 (0.57, 12.06)	0.0318[a]

CI = confidence interval; GO-QoL = Graves' Ophthalmopathy Quality of Life; LS = least squares

Note: For responder rates, a participant missing the week 24 evaluation was considered a non-responder.
Note: Results shown are those for the study eye for the change from baseline in proptosis at week 24 and proptosis responder rate.
[a] p-value is from mixed model repeated measurements analysis with an unstructured variance-covariance matrix including change from baseline value as the dependent variable and the following covariates: Baseline value, treatment group, visit, visit-by-treatment and visit-by-baseline value interactions.
[b] p-value is from Fisher exact test. Placebo was the reference group for the analysis.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with TEPEZZA in all subsets of the paediatric population with thyroid eye disease (see section 4.2 for information on paediatric use).

Immunogenicity

In a randomised placebo-controlled study (OPTIC) where teprotumumab was administered intravenously over a 24-week period to participants with active TED, 4.9% (2 of 41) participants tested positive for binding anti-drug antibodies at post-baseline visits. There was no apparent impact of ADA on efficacy, safety, or pharmacokinetics.

5.2 Pharmacokinetic properties

The pharmacokinetics of teprotumumab was described by a two-compartment population pharmacokinetic (PK) model. Based on data from 10 healthy subjects (dose of 1 500 mg) single intravenous and 176 patients with TED (first infusion at 10 mg/kg followed by 7 repeated doses of 20 mg/kg Q3W), teprotumumab follows dose-proportional pharmacokinetics. Following the recommended dose regimen (first infusion at 10 mg/kg followed by 7 repeated doses of 20 mg/kg Q3W), the mean (± SD) estimates for AUC_{ss}, peak $C_{max,ss}$, and trough $C_{min,ss}$ concentrations of teprotumumab were 139 (± 27) mg×hr/mL, 675 (± 147) mcg/mL, and 159 (± 38) mcg/mL, respectively.

Distribution

Following the recommended teprotumumab dosing regimen, the population PK estimated mean (± SD) for volume of distribution of teprotumumab were 6.76 (± 1.17) L.

Biotransformation

Metabolism of teprotumumab has not been fully characterised. However, teprotumumab is expected to undergo metabolism via proteolysis.

Elimination

Following the recommended teprotumumab dosing regimen, the population PK estimated mean (± SD) for the clearance of teprotumumab was 0.27 (± 0.07) L/day and for the elimination half-life was 22 (± 4) days.

Special populations

No clinically relevant differences in the pharmacokinetics of teprotumumab were observed following administration of teprotumumab based on patient's age (18–80 years), gender, ethnicity, renal function, bilirubin levels, aspartate aminotransferase (AST) levels, or alanine aminotransferase (ALT) levels. No dose adjustments are considered necessary for patients with renal and hepatic impairment (see section 4.2).

5.3 Preclinical safety data

In repeat-dose toxicity studies in cynomolgus monkeys, non-adverse, reversible thymic atrophy, decreased serum alkaline phosphatase and lower body weight gains occurred in animals at exposure similar to the exposure in humans at the proposed clinical dose.

Carcinogenicity and mutagenicity

Carcinogenic or mutagenic potential of teprotumumab was not evaluated.

Fertility

No male or female reproductive organ toxicity or histopathology findings were observed in repeat-dose toxicity studies in cynomolgus monkeys.

Embryo-foetal toxicity

In an embryo-foetal development study, seven pregnant cynomolgus monkeys were dosed intravenously at one dose level of teprotumumab (8.3-fold the maximum recommended human dose based on AUC) once weekly from gestation day 20 through the end of gestation. The incidence of abortion was higher for the teprotumumab-treated group (2 out of 7 foetuses, 28.6%) compared to the control group (1/6, 16.7%). Teprotumumab caused decreased foetal growth during pregnancy, decreased foetal size and weight at caesarean section, decreased placental weight and size, and decreased amniotic fluid volume. Multiple external and skeletal abnormalities were observed in each exposed foetus, including: misshapen cranium, closely set eyes, micrognathia, pointing and narrowing of the nose, and ossification abnormalities of skull bones, sternebrae, carpals, tarsals and teeth. The test dose was the maternal no observed adverse effect level.

Based on the mechanism of action of teprotumumab which is the inhibition of IGF-1R signalling, exposure to teprotumumab may cause harm to the foetus.

Toxicity in juvenile animals

In juvenile (11-14 months old) cynomolgus monkeys, teprotumumab treatment for 13 weeks resulted in decreased bone mass (bone mineral content and density), narrower bones with thinner cortices attributed to reduced periosteal expansion, and decreased body weight gains with some signs of reversibility after 13 weeks of recovery. These findings occurred at exposures similar to the exposure in human adults at the proposed clinical dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Histidine hydrochloride monohydrate
Polysorbate 20 (E432)
Trehalose dihydrate

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Lyophilised powder in unopened vial

3 years

Reconstituted and diluted infusion solution

Chemical and physical in-use stability of the reconstituted solution in the vial has been demonstrated for up to 4 hours at room temperature (20°C – 25°C) or up to 48 hours at 2°C to 8°C storage condition.

Chemical and physical in-use stability of the diluted solution in the infusion bag has been demonstrated for 24 hours at 2°C to 8ºC followed by 24 hours at room temperature (20°C – 25°C) storage condition.

From a microbiological point of view, 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 would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution and dilution has taken place in controlled and validated aseptic conditions. If refrigerated prior to administration, the diluted solution should be at room temperature prior to infusion.

6.4 Special precautions for storage

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

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

20 mL type I clear glass vial, with a grey stopper (flurotec coated chlorobutyl) and an aluminium seal with a polypropylene matte red flip-off cap.

Each carton contains one vial.

6.6 Special precautions for disposal and other handling

TEPEZZA should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared solution.

After reconstitution, teprotumumab is a nearly colourless or slightly brown, clear to opalescent solution which is free of foreign particulate matter. The reconstituted solution should be inspected for particular matter and discolouration prior to administration. The vial should be discarded if particulate matter is present or discolouration is observed. Refer to section 6.3 for stability after reconstitution.

Preparation of the medicinal product before administration

Step 1: Calculate the dose (mg) and determine the number of vials needed for the 10 or 20 mg/kg dose based on patient weight. Each vial contains 500 mg of teprotumumab.

Step 2: Using appropriate aseptic technique, reconstitute each vial with 10 mL of water for injections. Ensure that the stream of diluent is not directed onto the lyophilised powder, which has a cake-like appearance. Do not shake, but gently swirl the solution by rotating the vial until the lyophilised powder is dissolved. The reconstituted solution has a total volume of 10.5 mL. Withdraw 10.5 mL of reconstituted solution to obtain 500 mg. After reconstitution, the final concentration is 47.6 mg/mL.

Step 3: The reconstituted solution must be further diluted in sodium chloride 9 mg/mL (0.9%) solution for infusion, prior to infusion. To prepare the diluted solution, use 100 mL infusion bags for a dose less than 1 800 mg, and 250 mL infusion bags for a dose equal of greater than 1 800 mg. To maintain a constant volume in the infusion bag, a sterile syringe and needle should be used to remove the calculated volume equivalent to the amount of the reconstituted solution to be placed into the infusion bag. The volume of sodium chloride 9 mg/mL (0.9%) solution withdrawn must be discarded.

Step 4: Withdraw the required volume from the reconstituted vial(s) based on the patient's weight (in kg) and transfer into an intravenous bag containing sodium chloride 9 mg/mL (0.9%) solution for infusion. Mix the diluted solution by gentle inversion. Do not shake. If refrigerated prior to administration, allow the diluted solution to reach room temperature prior to infusion. Care should be taken to ensure the sterility of the prepared solution.

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

No incompatibilities between teprotumumab and polyethylene (PE), polyvinyl chloride (PVC), polyurethane (PUR) or polyolefin (PO) bags and intravenous administration sets have been observed.

7. MARKETING AUTHORISATION HOLDER

Amgen Europe B.V.
Minervum 7061
4817 ZK Breda
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1941/001

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 MANUFACTURERS 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 MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

AGC Biologics A/S
Vandtårnsvej 83B
Søborg 2860
Denmark

Name and address of the manufacturers responsible for batch release

Horizon Therapeutics Ireland DAC
Pottery Road
Dun Laoghaire
Dublin
A96 F2A8
Ireland

Amgen NV
Telecomlaan 5-7
1831 Diegem
Belgium

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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 Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months.

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 use of TEPEZZA 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:
- Provision of information to healthcare professionals for the risks of hearing impairment and embryo-foetal toxicity.
- Provision of information to patients for the risks of hearing impairment and embryo-foetal toxicity.

The MAH shall ensure that in each Member State where TEPEZZA is marketed, all healthcare professionals involved in the care of patients who will be treated with TEPEZZA have access to the following educational package:
- Healthcare professional educational material
- Patient information pack

Healthcare professional educational material:
- The Summary of Product Characteristics
- Healthcare professional guide

- **Healthcare professional guide**
  - What is known about the safety of TEPEZZA as it relates to hearing impairment and embryo-foetal toxicity.
  - Management of early signs and symptoms of hearing impairment.
  - Before a decision is made about treatment with TEPEZZA the doctor will discuss with the patient the following:
    - TEPEZZA may cause hearing impairment and details on the signs and symptom to look for.
    - Requirement for monitoring for hearing impairment and appropriate management.
    - The patient should seek medical advice as soon as possible if they experience changes in hearing.
    - TEPEZZA may cause harm to the unborn foetus.
    - Patients who are considering TEPEZZA treatment should inform the doctor if they are pregnant.
    - The importance of using appropriate contraception during treatment with TEPEZZA.

- Patients being treated with TEPEZZA should notify the doctor without delay if they become pregnant.
- The healthcare professional will provide the Patient Guide and the Package Leaflet to the patient.

The patient information pack:

- Package Leaflet
- Patient Guide

- **Patient Guide:**
  - Description of the risk of hearing impairment and the key signs and symptoms.
  - Description of what to do if signs and symptoms of hearing impairment occur.
  - Information about the physician's assessment of hearing before, during, and after treatment with TEPEZZA.
  - Instructions to seek medical attention if they have hearing problems or worsening of existing hearing problems.
  - Information on the risk of harm to an unborn child.
  - Instructions to inform the doctor if they are pregnant before starting treatment with TEPEZZA.
  - Instructions on appropriate contraception while being treated with TEPEZZA.
  - Instructions to notify the doctor without delay if they become pregnant while taking TEPEZZA.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

TEPEZZA 500 mg powder for concentrate for solution for infusion
teprotumumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 500 mg teprotumumab.
After reconstitution, each vial contains 47.6 mg/mL of teprotumumab.

3. LIST OF EXCIPIENTS

Histidine, histidine hydrochloride monohydrate, polysorbate 20 (E432), trehalose dihydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after reconstitution and dilution.
Read the package leaflet before use.

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

9. SPECIAL STORAGE CONDITIONS

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

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

Amgen Europe B.V.,
Minervum 7061,
4817 ZK Breda,
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1941/001

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

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT

TEPEZZA 500 mg powder for concentrate
teprotumumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 500 mg teprotumumab.
After reconstitution, each vial contains 47.6 mg/mL of teprotumumab.

3. LIST OF EXCIPIENTS

Histidine, histidine hydrochloride monohydrate, polysorbate 20 (E432), trehalose dihydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion.
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

IV after reconstitution and dilution
Read the package leaflet before use.

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 shelf life of the diluted medicine.

9. SPECIAL STORAGE CONDITIONS

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

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

Amgen Europe B.V.
Minervum 7061,
4817 ZK Breda,
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1941/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

TEPEZZA 500 mg powder for concentrate for solution for infusion
teprotumumab

▼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 using 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 or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What TEPEZZA is and what it is used for

TEPEZZA contains teprotumumab, a type of protein (monoclonal antibody).

This medicine is used in adults to treat moderate to severe thyroid eye disease (TED).

TED is an autoimmune condition where the immune system (the body's natural defences) attacks the muscles and fat around the eyes. A protein called IGF-1R is found in the muscles and fat around the eyes. In people with TED, the immune system activates IGF-1R, causing inflammation and swelling which can push the eyes forward, causing them to bulge. It can also result in double vision, and in severe cases, may cause permanent vision damage.

The active substance in TEPEZZA, teprotumumab, blocks the IGF-1R protein, this keeps the immune system from attacking the muscle and fat tissues around the eyes, which helps reduce swelling, relieve pressure around the eyes and improve disease symptoms.

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

Do not use TEPEZZA

- if you are allergic to teprotumumab or any of the other ingredients of this medicine (listed in section 6).
- if you are pregnant (see section 'Pregnancy, breast-feeding and contraception').

If you are not sure, talk to your doctor or nurse before being given TEPEZZA.

Warnings and precautions

Talk to your doctor or nurse before taking TEPEZZA if you:

- have history of hearing problems or if you use hearing aids
- are sensitive to loud noises
- have diabetes or pre-diabetes
- have inflammatory bowel disease
- are pregnant or planning to have a baby
- smoke
- ever had high blood pressure

You should stop smoking before starting treatment, and your doctor may need to monitor your blood pressure before and during treatment.

Your doctor will explain the benefits and risks of TEPEZZA and provide you with a 'Patient Guide' to help you understand the risk of developing hearing problems and the need for effective contraception during treatment.

Infusion-related reactions

You will be monitored during the infusion and for 90 minutes afterwards to check if you develop a reaction to the infusion. Tell your doctor or nurse if you develop symptoms of an infusion-related reaction, particularly if this occurs following the monitoring period. Symptoms of infusion-related reactions are listed under "Possible side effects" in section 4.

High blood sugar (hyperglycaemia)

TEPEZZA may cause blood sugar levels to increase, especially if you already have diabetes or pre-diabetes (see section 4 "Possible side effects").

Your doctor or nurse will check your blood sugar levels before you start treatment, during treatment, and for up to 6 months after you finish. If your blood sugar is not well controlled with your current diabetes medication, please speak to your doctor. It's important to make sure your blood sugar is properly managed before starting TEPEZZA treatment.

Hearing problems

TEPEZZA may cause problems with your hearing including severe hearing loss, which may be permanent. Symptoms of hearing problems are listed under "Possible side effects" in section 4. If you already have hearing problems, your symptoms may get worse during or after treatment. Contact your doctor as soon as possible if you notice any changes in your hearing at any time.

You should avoid loud noises during treatment. Your hearing will be monitored with a hearing test before starting treatment, during and after completing treatment.

Your doctor will decide if any additional hearing tests are needed and will monitor your hearing for 6 months after you complete treatment. If you experience hearing loss that requires medical treatment, affects your ability to perform everyday tasks, or is getting worse, your doctor may stop your treatment with TEPEZZA.

Inflammatory bowel disease

TEPEZZA may worsen existing inflammatory bowel disease (IBD); inflammation of the colon and rectum, including ulcerative colitis and Crohn's disease. During the treatment if you notice any signs of an IBD flare-up (see section 4), tell your doctor or seek medical help as soon as possible.

Children and adolescents

TEPEZZA is not recommended for children and adolescents under 18 years of age. The safety and benefit of this medicine have not been established in these patient populations.

Other medicines and TEPEZZA

Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription and herbal medicines.
It is important to tell your doctor if you are taking medicines that can affect your hearing, such as:

- certain antibiotics (e.g. aminoglycosides or vancomycin),
- Platinum-containing medicines used to treat cancer,
- water tablets (loop diuretics) used to remove excess fluid.

Using these together with TEPEZZA may increase the risk of hearing problems.

Pregnancy, breast-feeding and contraception

Pregnancy

If you think you may be pregnant or are planning to have a baby, ask your doctor or nurse for advice before using this medicine.

Do not use this medicine if you are pregnant. TEPEZZA may harm your unborn baby.

Contraception

If you are able to get pregnant you should use adequate birth control while you are being treated with TEPEZZA and for at least 6 months after your last treatment.

Breast-feeding

Do not use this medicine if you are breast-feeding. It is not known if this medicine passes into breast milk, and the risk to the breast-fed infant is unknown. If you plan to breast-feed, ask your doctor or nurse for advice before using this medicine.

Driving and using machines

While you are being treated with TEPEZZA you may experience fatigue or headaches. This may impair your ability to drive or use machines. Do not drive a car or operate machines if you have these symptoms.

TEPEZZA contains polysorbate

This medicine contains 1.05 mg of polysorbate 20 in each 10.5 mL volume. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How TEPEZZA is given

This medicine is given in a healthcare facility under the supervision of a healthcare professional.

You will receive eight infusions given once every three weeks. The dose of TEPEZZA depends on your body weight.

A doctor or nurse will give you this medicine as an intravenous infusion (drip into your vein). Your doctor will decide the duration of the infusion.

If too much TEPEZZA is given

TEPEZZA is given to you by healthcare professionals and it is unlikely that you will be given too much. If this happens, your doctor will monitor you for any signs or symptoms of side effects and treat these symptoms if necessary.

If a dose of TEPEZZA is missed

If you miss a dose, please contact your doctor immediately for advice and to schedule another appointment to receive TEPEZZA. Your doctor will decide when you should be given your next dose.

If you stop treatment with TEPEZZA

Do not stop treatment with TEPEZZA unless you have discussed this with your doctor.

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

4. Possible side effects

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

Tell your doctor or nurse immediately if you experience any of the following symptoms during or after the infusion:

Infusion-related reactions (Common, may affect up to 1 in 10 people)

You may experience symptoms such as:
- difficulty in breathing or chest pain
- redness or flushing of the skin or a rash
- chills or shivering
- feeling of being sick
- light headedness
- fast heartbeat
- loss of consciousness

Contact a doctor or go to your nearest emergency department immediately if you experience any of the following symptoms:

<u>Very high blood sugar (hyperglycaemia)</u>

TEPEZZA may cause uncontrolled high blood sugar, especially if you already have diabetes or pre-diabetes. Tell your doctor, nurse or go to your nearest emergency department immediately if you experience signs of very high blood sugar, including:

- diabetic ketoacidosis (uncommon, may affect up to 1 in 100 people) - a potentially life-threatening condition in people with diabetes where a lack of insulin causes an increase in blood sugar levels and ketones. Early symptoms include feeling very thirsty and urinating more often than usual. You may experience other symptoms such as nausea, vomiting, feeling tired or confused, stomach pain, faster or deeper breathing, and fruity-smelling breath.
- hyperosmolar hyperglycaemic state (not known, frequency cannot be estimated from the available data) - a serious condition that occurs when blood sugar becomes extremely high over several days or weeks, leading to severe dehydration and confusion.

Contact a doctor as soon as possible if you experience any of the following symptoms:

Hearing problems

You may experience symptoms such as:

Common (may affect up to 1 in 10 people)
- feeling of blocked ears, or pressure in the ear (ear discomfort)
- partial or total loss of hearing
- ringing or buzzing in the ears (tinnitus)
- hearing your own voice louder than normal
- muffled hearing

Uncommon (may affect up to 1 in 100 people)
- damage to the ear drum
- increased sensitivity to particular sounds

Worsening of inflammatory bowel disease (Uncommon, may affect up to 1 in 100 people)

The symptoms may include an increased number of loose stools with stomach pain or cramps, or blood in your stools.

See also section 2 “Warnings and precautions” for more information.

Other side effects:

Most of the following side effects are mild to moderate.

Very common (may affect more than 1 in 10 people)
- muscle cramps
- diarrhoea
- hair loss
- feeling extremely tired or lacking energy
- feeling sick (nausea)
- headache

Common (may affect up to 1 in 10 people)
- dry skin
- change in the sense of taste
- COVID-19
- high blood sugar
- weight loss
- diabetes mellitus
- nail splitting, breaking, or coming away from the nail bed
- loss of eyebrows or eyelashes
- pre-diabetes
- nail discolouration
- missing one or more periods
- irregular periods
- heavy periods
- lighter periods
- pain or cramping during your period

Uncommon (may affect up to 1 in 100 people)
- ingrown nail

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. 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 TEPEZZA

TEPEZZA will be stored by the healthcare professionals at the hospital or clinic.

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 outer carton and on the vial label after EXP. The expiry date refers to the last day of that month.

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

6. Contents of the pack and other information

What TEPEZZA contains

- The active substance is teprotumumab.
- Each vial contains 500 mg teprotumumab.

The other ingredients are histidine, histidine hydrochloride monohydrate, polysorbate 20 (E432) and trehalose dihydrate. See section 2 “TEPEZZA contains polysorbate”.

What TEPEZZA looks like and contents of the pack

TEPEZZA is a powder for concentrate for solution for infusion, which is supplied in a glass vial with a rubber stopper containing 500 mg of teprotumumab. The powder is a white to off white powder supplied in a single-dose vial. Each pack contains one vial.

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Other sources of information

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

The following information is intended for healthcare professionals only:

Posology and method of administration

TEPEZZA should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared solution.

Preparation of the medicinal product before administration

Step 1: Calculate the dose (mg) and determine the number of vials needed for the 10 or 20 mg/kg dose based on patient weight. Each TEPEZZA vial contains 500 mg of teprotumumab.

Step 2: Using appropriate aseptic technique, reconstitute each vial with 10 mL of water for injections. Ensure that the stream of diluent is not directed onto the lyophilised powder, which has a cake-like appearance. Do not shake, but gently swirl the solution by rotating the vial until the lyophilised powder is dissolved. The reconstituted solution has a total volume of 10.5 mL. Withdraw 10.5 mL of reconstituted solution to obtain 500 mg. After reconstitution, the final concentration is 47.6 mg/mL.

Step 3: The reconstituted solution must be further diluted in sodium chloride 9 mg/mL (0.9%) solution for infusion, prior to infusion. To prepare the diluted solution, use 100 mL infusion bags for a dose less than 1 800 mg, and 250 mL infusion bags for a dose equal of greater than 1 800 mg. To maintain a constant volume in the infusion bag, a sterile syringe and needle should be used to remove the volume equivalent to the amount of the reconstituted solution to be placed into the infusion bag. The volume of sodium chloride 9 mg/mL (0.9%) solution withdrawn must be discarded.

Step 4: Withdraw the required volume from the reconstituted vial(s) based on the patient's weight (in kg) and transfer into an intravenous bag containing sodium chloride 9 mg/mL (0.9%) solution for infusion. Mix the diluted solution by gentle inversion. Do not shake. If refrigerated prior to administration, allow the diluted solution to reach room temperature prior to infusion. Care should be taken to ensure the sterility of the prepared solution.

No incompatibilities between teprotumumab and polyethylene (PE), polyvinyl chloride (PVC), polyurethane (PUR) or polyolefin (PO) bags and intravenous administration sets have been observed.

Appearance on reconstitution

After reconstitution, TEPEZZA is a nearly colourless or slightly brown, clear to opalescent solution which is free of foreign particulate matter. The reconstituted solution should be inspected for particular matter and discolouration prior to administration. Discard the solution if particulate matter is present or discolouration is observed.

Storage of reconstituted and diluted infusion solution

Chemical and physical in-use stability of the reconstituted solution in the vial has been demonstrated for up to 4 hours at room temperature (20°C – 25°C) or up to 48 hours at 2°C to 8°C storage condition.

Chemical and physical in-use stability of the diluted solution in the infusion bag has been demonstrated for 24 hours at 2°C to 8ºC followed by 24 hours at room temperature (20°C – 25°C) storage condition.

From a microbiological point of view, 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 would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution and dilution has taken place in controlled and validated aseptic conditions. If refrigerated prior to administration, the diluted solution should be at room temperature prior to infusion.

Method of administration

- This medicinal product must be administered as an intravenous infusion. It must not be administered as an intravenous push or bolus.
- Prior to infusion:
  - the powder must be reconstituted with water for injections.
  - The reconstituted solution must be further diluted in sodium chloride 9 mg/mL (0.9%) solution for infusion.
- TEPEZZA must not be co-administered with other medicinal products through the same infusion line.
- For the first 2 infusions, the diluted solution must be administered intravenously over at least 90 minutes. If well tolerated, the minimum time for subsequent infusions can be reduced to 60 minutes.
- If the 60-minute infusion is not well tolerated, the minimum time for subsequent infusions should remain at 90 minutes, the rate of infusion should be reduced and pre-medication is recommended for subsequent infusions.

Special precautions for disposal and other handling

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