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 an insulin-like growth factor-1 receptor inhibitor (IGF-1R), is a fully human IgG1 monoclonal antibody produced in Chinese Hamster Ovary (CHO-DG44) cells by recombinant DNA technology.

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

This medicine 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.

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) (see section 5.1).

4.2 Posology and method of administration

TEPEZZA must be administered as an intravenous infusion via an infusion pump.

TEPEZZA must be administered by a healthcare professional and under the supervision of a physician experienced in the diagnosis and treatment of TED with access to appropriate medical support to manage potential severe reactions such as serious infusion-related reactions.

Posology

TEPEZZA dosing is based on the patient's actual body weight. The recommended dose of TEPEZZA 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. Available data suggest that clinical response is usually achieved within 8 doses of treatment.

Recommended pre-medication

For patients experiencing immediate hypersensitivity reactions or infusion-related reactions during the first two infusions of TEPEZZA, 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

Based on the available clinical data, no dose adjustment is considered necessary in patients over 65 years old (see section 5.2). There is no data in those over 80 years of age.

Renal impairment

No clinically significant differences in the pharmacokinetics of TEPEZZA were observed following administration of TEPEZZA to patients with mild to moderate renal impairment (see section 5.2).

No dose adjustment is considered necessary in patients with mild to moderate renal impairment.

Hepatic impairment

The effect of hepatic impairment on the pharmacokinetics of TEPEZZA is unknown. However, no clinically significant differences in the pharmacokinetics of TEPEZZA were observed following administration of TEPEZZA to patients with elevated bilirubin levels aspartate aminotransferase (AST) levels, or alanine aminotransferase (ALT) levels (see section 5.2).

Paediatric population

The safety and efficacy of TEPEZZA in children < 18 years of age has not been established. No data are available (see section 5.1).

Method of administration

- TEPEZZA must be administered as an intravenous infusion via an infusion pump.
- Prior to infusion:
  - TEPEZZA must be reconstituted with water for injections
  - The reconstituted TEPEZZA solution must be further diluted in sodium chloride 9 mg/mL (0.9%) solution for infusion, prior to infusion
- TEPEZZA must not be co-administered with other medicinal products through the same infusion line.
- TEPEZZA must not be administered as an intravenous push or bolus.
- For the first 2 infusions, administer the diluted solution intravenously over at least 90 minutes. If well tolerated, the minimum time for subsequent infusions can be reduced to 60 minutes.
- If 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

TEPEZZA may cause infusion reactions. Infusion reactions have been reported in approximately 4% of patients treated with TEPEZZA (see section 4.8). Patients should be advised to contact their healthcare professionals if they experience signs and symptoms of infusion-related reactions including but not limited to transient increases in blood pressure, feeling hot, tachycardia, dyspnoea, headache and muscular pain. Patients should be monitored closely throughout the infusion and for 90 minutes after completion of the infusion. Based on the severity of the infusion-related reaction, TEPEZZA 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. For patients who experience an anaphylactic reaction, discontinue TEPEZZA immediately and permanently.

Hyperglycaemia

Hyperglycaemia or increased blood glucose may occur in patients treated with TEPEZZA. In double -masked TED clinical trials, 13.2% of patients (80% of whom had pre-existing diabetes or impaired glucose tolerance) experienced hyperglycaemia. Adverse events associated with hyperglycaemia may include diabetes mellitus, diabetic ketoacidosis, glucose tolerance impaired, glycosylated haemoglobin increased and a hyperosmolar hyperglycaemic state. Hyperglycaemic events should be managed with medications for glycaemic control, if necessary.

Assess patients for elevated blood glucose and symptoms of hyperglycaemia prior to infusion and continue to monitor while on treatment with TEPEZZA. Ensure patients with hyperglycaemia or pre-existing diabetes are under appropriate glycaemic control before and while receiving TEPEZZA (see section 4.8). Blood glucose monitoring is recommended for 6 months after completion of treatment with teprotumumab.

Hearing impairment

TEPEZZA 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, including neurosensory hypoacusis, deafness unilateral, eustachian tube dysfunction, eustachian tube patulous, hyperacusis, hypoacusis, autophony, tinnitus and tympanic membrane disorder), have been observed in clinical trials (13.8%) and post-marketing experience with TEPEZZA (see section 4.8).

Assess patients' hearing before, during and after treatment with TEPEZZA.

For patients with pre-existing hearing impairment, the benefit-risk of treatment should be considered.

The benefit-risk of continuing treatment with TEPEZZA should be reconsidered in patients who experience severe hearing impairment during the treatment. Patients should be advised to stop smoking and avoid high intensity noises during treatment with TEPEZZA.

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

Exacerbation of pre-existing inflammatory bowel disease (IBD)

TEPEZZA may cause an exacerbation of pre-existing inflammatory bowel disease (IBD). Monitor patients with IBD for flare of disease. If IBD exacerbation is suspected, consider discontinuation of TEPEZZA. Patients with pre-existing inflammatory bowel disease were excluded from clinical studies (see section 4.8).

Concomitant therapies

Caution is needed when co-administering TEPEZZA 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.

Information about excipients

This medicine 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 TEPEZZA 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 highly effective contraception while receiving TEPEZZA and for 6 months after the last administration of TEPEZZA.

Pregnancy

There are no adequate data from the use of teprotumumab in pregnant women. No human developmental and reproductive studies were conducted with teprotumumab.

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

Based on the mechanism of action inhibiting IGF-1R and the teratogenic effects observed in animal developmental studies, TEPEZZA 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. There are no data on the use of TEPEZZA in breast-feeding women and a risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to abstain from TEPEZZA therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

The effects of TEPEZZA in humans are unknown. Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions observed in clinical trials are; muscle spasms (27.6%), diarrhoea (14.5%), hearing impairment (13.8%), alopecia (13.2%), hyperglycaemia (13.2%), fatigue (12.5%), nausea (10.5%), headache (10.5%), dry skin (9.9%), dysgeusia (8.6%), COVID-19 (6.6%), ear discomfort (6.6%) and nail disorder (5.9%).

The most common serious adverse reactions are; diarrhoea, inflammatory bowel disease, infusion -related reaction.

Tabulated list of adverse reactions

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 medicines or unrelated causes.

Adverse reactions reported in clinical trials and derived from spontaneous reporting are listed below in table 1. The adverse reactions are listed by MedDRA System Organ Class and by frequency. The frequencies of adverse reactions is based on 4 placebo-controlled studies with 285 patients. Patients were exposed to teprotumumab for a median of 148 days.

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).

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 (> 1/1 0 000 to < 1/1 0 00)	Not known/cannot be estimated from available data
Infections and infestations		COVID-19			
Metabolism and nutrition disorders	Hyperglycaemia[1]		Diabetic ketoacidosis		Hyperosmolar hyperglycaemic state[2]
Nervous system disorders	Headache	Dysgeusia			
Ear and labyrinth disorders		Ear discomfort, Autophony, Deafness, Eustachian tube dysfunction, Eustachian tube patulous, Hypoacusis, Neurosensory hypoacusis, Tinnitus	Conductive deafness, Deafness unilateral, Hyperacusis, Tympanic membrane disorder		
Gastrointestinal disorders	Diarrhoea Nausea		Inflammatory bowel disease[1]		
Skin and subcutaneous tissue disorders	Alopecia	Dry skin Nail bed disorder, Nail discoloration, Onychoclasis	Ingrowing nail		
Musculoskeletal and connective tissue disorders	Muscle spasms				
Reproductive system and breast disorders		Amenorrhea, Hypomenorrhea, Dysmenorrhea, Irregular menstruation, 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 usually mild or moderate in intensity and can be successfully managed with antihistamines and/or corticosteroids, if needed. No infusion-related reactions in TED trials were reported as anaphylactic reactions. See sections 4.2 and 4.4 for action to be taken in case of infusion -related reactions.

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.

Hyperglycaemia

In clinical trials, all hyperglycaemia events reported in teprotumumab-treated patients were mild or moderate in severity. In the completed clinical trials, all events resolved. The mean time to onset of hyperglycaemia events was 67.8 days (range: 1 to 169 days) from first infusion of TEPEZZA. One serious event of Diabetic ketoacidosis was reported in a patient from the placebo group who received a single dose of TEPEZZA. This event was severe and resolved. The time to onset for this event was 20 days. Recommendations for management of hyperglycaemia are provided in section 4.4.

Hearing impairment

In clinical trials, the majority of hearing impairment events reported in teprotumumab-treated patients were mild or moderate in severity. The mean time to onset of hearing impairment events was 77.9 days (range: 3 to 153 days). One serious event of conductive deafness was reported for a teprotumumab-treated patient. This event was severe, led to discontinuation of Teprotumumab and did not resolve. The time to onset for this event was 152 days.

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:

Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

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 antiboides, ATC code: L04AG13

Mechanism of action

Teprotumumabs mechanism of action in patients with Thyroid Eye Disease (TED) has not been fully characterised. Teprotumumab binds to the insulin-like growth factor-1 receptor (IGF-1R) and blocks its activation and signalling. No formal pharmacodynamic studies have been conducted with teprotumumab.

Pharmacodynamic effects

No formal pharmacodynamic studies have been conducted with teprotumumab.

Clinical efficacy and safety

The efficacy and safety of teprotumumab was assessed in 287 patients with thyroid eye disease in four randomised, double-masked, placebo-controlled clinical studies. The classification of severity of thyroid eye disease used in these studies were consistent with the European Group on Graves' Orbitopathy (EUGOGO) criteria.

TED01RV was a randomized, double-masked, placebo-controlled study in patients with acute TED. Patients were randomized to receive TEPEZZA or placebo in a 1:1 ratio. Patients were given intravenous infusions (10 mg/kg for first infusion and 20 mg/kg for the remaining 7 infusions) every 3 weeks for a total of 8 infusions. Patients had a clinical diagnosis of TED with symptoms and were euthyroid or had thyroxine and free triiodothyronine levels less than 50% above or below normal

limits. Prior surgical treatment for TED was not permitted. Median proptosis was 23 mm and ranged from 16 to 33 mm and 69 patients (79.3%) had diplopia at baseline. The median clinical activity score (CAS) on the study eye at baseline was 5 (range 2 to 7) and the median time since the diagnosis of TED was 5.76 months (range 1.2 to 11.0).

A total of 43 patients were randomized to TEPEZZA and 45 patients were randomized to placebo. The median age was 52.9 years (range 20.4 to 77.0), 73.6% were female and 66.7% were non-smokers. 86.2% were white, 9.2% were black, 3.4% were Asian, and 1.1% were native Hawaiian or other Pacific Islander.

TEPEZZA demonstrated a statistically significant improvement in the primary endpoint, overall responder rate at week 24 (defined as the proportion of patients with a decrease in CAS of ≥ 2 points and a reduction of proptosis ≥ 2 mm in the study eye without deterioration in the fellow eye) (See Table 2).

Table 2. Overall Responder Rate at Week 24 in TED01RV (ITT Analysis Set)

Primary Endpoint	**Placebo (N = 45)**	**TEPEZZA (N = 42)**	**Odds Ratio (95% CI) TEPEZZA vs Placebo**	**p-value**
Overall Responder, n (%)	9 (20.0)	29 (69.0)	8.86 (3.293, 23.825)	< 0.001

CI= Confidence Interval; ITT = intent-to-treat
Odds ratio, 95% CI, and p-value were obtained from a logistic regression model with treatment a smoking status as covariates.

OPTIC was a randomized, double-masked, placebo-controlled study in patients with acute TED. Patients were randomized to receive either TEPEZZA or placebo in a 1:1 ratio. Patients were given intravenous infusions (10 mg/kg for the first infusion and 20 mg/kg for the remaining 7 infusions) every 3 weeks for a total of 8 infusions. Patients had a clinical diagnosis of TED within 9 months of enrolment in the study with symptoms and were euthyroid or had thyroxine and free triiodothyronine levels less than 50% above or below normal limits. Prior surgical treatment for TED was not permitted. Median proptosis was 23 mm and ranged from 16 to 33 mm and 56 patients (67.5%) had diplopia at baseline. The median clinical activity score (CAS) on the study eye at baseline was 5 (range 4 to 7) and the median time since the diagnosis of TED was 6.78 months (range 0.9 to 10.3).

A total of 41 patients were randomized to TEPEZZA and 42 were randomized to placebo. The median age was 52.0 years (range 20 to 79), 72.3% were female and 79.5% were non-smokers. 86.7% were white, 7.2% were black, 3.6% were Asian, and 2.4% were categorized as other.

TEPEZZA demonstrated a statistically significant improvement in the primary endpoint, 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 (see Table 3).

Table 3. Proptosis Responder Rate at Week 24 in OPTIC (ITT Analysis Set)

Primary Endpoint	**Placebo (N = 42)**	**TEPEZZA (N = 41)**	**Treatment Difference (95% CI)**	**p-value**
Proptosis Responder Rate, n (%)	4 (9.5)	34 (82.9)	73.45 (58.89, 88.01)	< 0.001[a]

CI = confidence interval; ITT = intent-to-treat

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

OPTIC-J was a randomized, double-masked, placebo-controlled study in Japanese patients with acute TED. Patients were randomized to receive either TEPEZZA or placebo in a 1:1 ratio. Patients were given intravenous infusions (10 mg/kg for the first infusion and 20 mg/kg for the remaining 7 infusions) every 3 weeks for a total of 8 infusions. Patients had a clinical diagnosis of TED within 9 months of enrolment in the study with symptoms and a CAS ≥ 3 (on the 7 item scale) for the most severely affected eye and were euthyroid or had thyroxine and free triiodothyronine levels < 50% above or below normal limits. Prior orbital irradiation or surgical therapy for TED was not permitted. Median proptosis was 20.0 mm and ranged from 14.5 to 27.0 mm and 42 patients (77.8%) had diplopia at baseline. The median clinical activity score (CAS) in the study eye at baseline was 4.0 (range 3 to 7) and the median time since the diagnosis of TED was 4.72 months (range 0.53 to 8.9).

A total of 27 patients were randomized to TEPEZZA and 27 were randomized to placebo. The median age was 49.0 years (range 20 to 74), 70.4% were female, and 85.2% were non-smokers and 100.0% were Asian.

TEPEZZA demonstrated a statistically significant improvement for the primary efficacy endpoint (proptosis responder rate at week 24 defined as a ≥ 2-mm reduction from baseline in proptosis in the study eye without deterioration [≥ 2-mm increase] of proptosis in the fellow eye). (See Table 4).

Table 4. Proptosis Responder Rate at Week 24 in OPTIC-J (ITT Analysis Set)

Primary Endpoint	**Placebo (N = 27)**	**TEPEZZA (N = 27)**	**Treatment Difference (95% CI)**	**p-value**
Proptosis responder rate at Week 24, n (%)	3 (11.1)	24 (88.9)	77.78 (60.7, 94.8)	< 0.0001[a]

CI = confidence interval; ITT = intent-to-treat

Note: Results shown are those for the study eye, if applicable.

[a] p-value was estimated from Cochran-Mantel-Haenszel test adjusted for the randomization stratification factor (tobacco use status).

HZNP-TEP-403 was a randomized, double-masked, placebo-controlled study in patients with chronic (inactive) TED. Patients were randomized to receive TEPEZZA or placebo in a 2:1 ratio. Patients were given intravenous infusions (10 mg/kg for first infusion and 20 mg/kg for the remaining 7 infusions) every 3 weeks for a total of 8 infusions.

Patients had an initial diagnosis of TED ≥ 2 years but < 10 years prior to screening and clinical diagnosis of stable TED defined as a CAS ≤ 1 in both eyes prior to screening for at least 1 year or all of the following for at least 1 year before screening: no proptosis progression, no diplopia progression in patients with history of diplopia, and no new inflammatory TED symptoms. Patients also had proptosis ≥ 3-mm increase from the participant's baseline (prior to diagnosis of TED) and/or proptosis ≥ 3 mm above normal for race and gender. Patients were euthyroid or had mild hypo- or hyperthyroidism. Previous orbital irradiation, orbital decompression or strabismus surgery or planned orbital irradiation or surgery for TED during this trial were not permitted. The median baseline proptosis was 25.0 mm and ranged from18.5 to 31.0 mm and 18 patients (29%) had diplopia at baseline. The median clinical activity score (CAS) on the study eye at baseline was 0 (range 0 to 1) and the median time since the diagnosis of TED was 5.39 years (range 2.24 to 8.74).

A total of 42 patients were randomized to TEPEZZA and 20 patients were randomized to placebo. The median age was 49.0 years (range 18 to 75), 80.6% were female, and 87.1% were non-smokers. 54.8% were white, 24.2% were black, 12.9% were Asian, and 8.1% were classified as other.

TEPEZZA demonstrated a statistically significant improvement in the primary endpoint, change from baseline in proptosis at week 24 in the study eye. (see Table 5).

Table 5. Change from baseline in proptosis at week 24 (study eye) **in HZNP-TEP-403 (ITT Analysis Set)**

Primary Endpoint	**Placebo (N = 20)**	**TEPEZZA (N = 42)**	**Treatment Difference (95% CI)**	**p-value**
Change from baseline in proptosis at Week 24 in the study eye, LS mean (SE)	-0.92 (0.323)	-2.41 (0.228)	-1.48 (-2.28, -0.69)	0.0004[a]

CI = confidence interval; ITT = intent-to-treat; LS = least squares; SE = standard error.
Note: Results shown are those for the study eye, if applicable.
[a] p-value is from mixed effect repeated measurement 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. A change from baseline value of 0 was imputed at the first post-baseline visit for any participant without post-baseline values.

Paediatric population

The Medicines and Healthcare products Regulatory 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

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease.

Following 8 intravenous (IV) infusions of teprotumumab in study HZNP-TEP-301 4.9% (2/41) had detectable levels of anti-drug antibodies. The presence of ADAs did not impact pharmacokinetics, efficacy or safety.

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 IV and 176 patients with TED (first infusion at 10 mg/kg followed by 7 repeated doses of 20 mg/kg every 3 weeks). Following the recommended dose regimen (first infusion at 10 mg/kg followed by 7 repeated doses of 20 mg/kg every 3 weeks), the mean (±SD) estimates for AUC_{ss}, peak C_{max}, and C_{trough} concentrations of teprotumumab were 139 (±27) mg*hr/mL, 675 (±147) µg/mL, and 159 (±38) µg/mL, respectively.

Distribution

Following the recommended teprotumumab dosing regimen, the population PK estimated mean (± standard deviation) for central and peripheral volume of distribution of teprotumumab were 3.01 (±0.77) L and 3.76 (± 0.60) L, respectively.

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 (± standard deviation) 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 significant differences in the pharmacokinetics of teprotumumab were observed following administration of teprotumumab based on patient's age (18-80 years), gender, race/ethnicity, weight, mild to moderate renal impairment, bilirubin levels, aspartate aminotransferase (AST) levels, or alanine aminotransferase (ALT) levels. The effect of hepatic impairment on the pharmacokinetics of teprotumumab is unknown.

5.3 Preclinical safety data

In adult cynomolgus monkeys, reversible thymic atrophy occurred in animals at doses resulting in exposures similar to and above that expected in humans but reversed on stopping dosing and did not lead to any effects on peripheral lymphoid cell counts or infections.

Juvenile (11-14 months old) cynomolgus monkeys were dosed once weekly with teprotumumab for 13 weeks with intravenous doses similar to the adult human clinical dose. These doses 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 in juvenile monkeys, with some signs of reversibility after 13 weeks of recovery.

Reversible thymic atrophy, decreased serum alkaline phosphatase and lower body weight gains occurred in animals at 2.6-fold the maximum human clinical exposure.

Carcinogenesis and mutagenesis

There have been no studies to assess the carcinogenic or mutagenic potential of teprotumumab.

Reproductive toxicity

No reproductive organ toxicity or histopathology findings were observed in any repeat dose toxicity studies for male or female cynomolgus monkeys. In an embryofoetal development study there was no maternal toxicity observed and the maternal no observed adverse event level (NOAEL) was considered the 75 mg/kg/week dose level for teprotumumab.

Pregnancy and developmental toxicity

In an embryofoetal development study, seven pregnant cynomolgus monkeys were dosed intravenously at one dose level of teprotumumab, 75 mg/kg (2.8-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, 75 mg/kg/week of teprotumumab, 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine

Histidine hydrochloride monohydrate

Polysorbate 20 (E432)

Trehalose dihydrate

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

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

6.3 Shelf life

Lyophilised powder in unopened vial

4 years

Reconstituted and diluted infusion solution

The product does not contain any preservative. Diluted infusion solution should be used immediately. If not used immediately the diluted solution in the infusion bag containing sodium chloride 9 mg/mL (0.9%) can be stored for up to 4 hours at 20°C to 25°C, protected from light or up to 48 hours at 2°C to 8°C, protected from light. The combined storage time of reconstituted solution in the vial and the diluted solution in the infusion bag containing 0.9% sodium chloride injection, is a total of 4 hours at room temperature 20°C to 25°C or up to 48 hours under refrigerated conditions 2°C to 8°C protected from light. If refrigerated prior to administration, allow the diluted solution to reach 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 preparation for infusion of the medicinal product, see section 6.3.

6.5 Nature and contents of container

TEPEZZA is supplied in 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

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

After reconstitution, teprotumumab is a 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. 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 dosage based on patient weight. Each TEPEZZA vial contains 500 mg of the teprotumumab antibody.

Step 2: Using appropriate aseptic technique, reconstitute each TEPEZZA vial with 10 mL of sterile water for injection. 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 TEPEZZA 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 TEPEZZA solution to be placed into the infusion bag. Discard the volume of sodium chloride 9 mg/mL (0.9%) solution for infusion withdrawn.

Step 4: Withdraw the required volume from the reconstituted TEPEZZA 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 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.

7 MARKETING AUTHORISATION HOLDER

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