EUROPEAN UNION RISK MANAGEMENT PLAN

Tepezza® (teprotumumab)

Marketing Authorization Applicant:	Amgen Europe B.V. Minervum 7061 4817 ZK Breda, Netherlands
Version:	1.0
Date:	24 April 2025
Supersedes:	Version 0.4, dated 18 April 2025

Risk Management Plan (RMP) version to be assessed as part of this application

RMP version number:	1.0
Data lock point of this RMP:	20 July 2024
Date of final sign-off:	24 April 2025
Rationale for submitting an updated RMP:	Not applicable

Summary of significant changes in this RMP

Part/Module/Annex	Major Change(s)	Version Number and Date
Part III: Pharmacovigilance Plan (Including Postauthorization Safety Studies)	Updated the draft protocol and feasibility report submission date for the 'Drug utilization study.'	Version 1.0; 24 April 2025
Part VII: Annexes		
Annex 2: Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program	Updated per change listed above.	Version 1.0; 24 April 2025

Other RMP versions under evaluation:	
RMP version number:	Not applicable
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Qualified Person for Pharmacovigilance (QPPV) Name:	Raphaël Van Eemeren, MSc Pharm and MSc Ind, Pharm
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorization applicant´s QPPV. The electronic signature is available on file.

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List of Abbreviations

Term/Abbreviation	Explanation
aRMM	additional risk minimization measure
ATC	Anatomical Therapeutic Chemical
CHO	Chinese hamster ovary
DKA	diabetic ketoacidosis
EEA	European Economic Area
EPAR	European Public Assessment Report
EU	European Union
EUGOGO	European Group On Graves' Orbitopathy
FDA	Food and Drug Administration
GI	gastrointestinal
HHS	hyperosmolar hyperglycemic state
IBD	inflammatory bowel disease
IGF-1	insulin-like growth factor-1
IGF-1R	insulin-like growth factor-1 receptor
IgG1	immunoglobulin G1
INN	International Nonproprietary Name
IV	intravenous
LDL	low density lipoprotein
mAb	monoclonal antibody
PI	Product Information
QPPV	Qualified Person for Pharmacovigilance
RAI	radioactive iodine
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TBD	to be determined
TED	thyroid eye disease
TRAb	thyrotropin receptor antibody
UK	United Kingdom
US	United States

PART I. PRODUCT(S) OVERVIEW

Table 1. Product(s) Overview

Active substance(s) (International Nonproprietary Name [INN] or common name)	Teprotumumab
Pharmacotherapeutic group (Anatomical Therapeutic Chemical [ATC] Code)	Immunosuppressants, monoclonal antibodies (L04AG13)
Marketing authorization applicant	Amgen Europe B.V.
Medicinal products to which this Risk Management Plan (RMP) refers	1
Invented name(s) in the European Economic Area (EEA)	Tepezza®
Marketing authorization procedure	Centralized
Brief description of the product	
Chemical class	Immunosuppressant
Summary of mode of action	Teprotumumab is an insulin-like growth factor-1 receptor (IGF-1R) inhibitor. Teprotumumab binds to IGF-1R and blocks its activation and signaling. Teprotumumab's mechanism of action in patients with thyroid eye disease (TED) has not been fully characterized.
Important information about its composition	Teprotumumab is a fully human immunoglobulin G1 (IgG1) monoclonal antibody produced in Chinese hamster ovary cells by recombinant DNA technology.
Hyperlink to the Product Information (PI)	The proposed PI is provided in Module 1.3.1.
Indication(s) in the EEA	
Current	Tepezza is indicated in adults for the treatment of moderate to severe Thyroid Eye Disease (TED).
Proposed	Not applicable.
Dosage in the EEA	
Current	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 3 weeks as an intravenous infusion.
Proposed	Not applicable.

Table 1. Product(s) Overview

Pharmaceutical form(s) and strength(s)	
Current	Tepezza is supplied as white to off-white lyophilised powder for concentrate for solution for infusion. Each vial contains 500 mg of teprotumumab. The reconstituted solution contains 47.6 mg/mL (500 mg/10.5 mL) of teprotumumab.
Proposed	Not applicable.
Is/will the product be subject to additional monitoring in the European Union (EU)?	Yes

PART II. SAFETY SPECIFICATION

Part II: Module SI - Epidemiology of the Indication(s) and Target Population(s)

Table 2. Summary of Epidemiology of Thyroid Eye Disease

Incidence	According to the European Group on Graves' orbitopathy (EUGOGO), the estimated incidence of TED is 0.54 to 0.9 cases per 100 000/year in men and 2.67 to 3.3 cases per 100 000/year in women. Mild and nonprogressive cases are common, and moderate to severe cases only account for 5 to 6% of all TED patients (Bartalena et al, 2021; Bartalena et al, 2020; Perros et al, 2015). The estimated incidence of moderate to severe TED in Europe is 0.161 per 10 000/year with a median age at onset of 50 years according to a large study from Denmark based on 8.9 million person-years of observation from 1992 to 2009 (Laurberg et al, 2012)
Prevalence	The estimated overall prevalence of TED in Europe from EUGOGO was 89.7 per 100 000 population. The prevalence of moderate to severe TED was 29.6 to 44.5 per 100 000 population (Perros, 2017).
Demographics of population in the proposed indication and risk factors for the disease	Specific European demographic data regarding TED is scarce. Other regions are relevant in terms of demographics given the wide ranging ethnicities present in the overall European population. Risk factors for TED are age, female gender, smoking, and diabetes mellitus type 1 (Lee et al, 2021). Elderly active smoking men have more severe TED. Highest prevalence is observed in 50 to 59 years age group. Limited evidence suggests African-Americans and Whites may be at relatively higher risk compared to Asians (Ramesh et al, 2023). Published studies reported thyrotropin receptor antibodies (TRAb) levels are associated with TED activity and severity (Nicolì et al, 2021; Bartalena et al, 2003, Gerding et al, 2000) and multiple studies reported serum total and low density lipoprotein (LDL) cholesterol levels were higher in patients with TED than in those without TED (Lanzolla et al, 2018; Sabini et al, 2018). An unstable thyroid function (hyperthyroidism and hypothyroidism) represents an important risk factor for the occurrence of TED (Hiromatsu et al, 2014). Thyroid eye disease is associated with an increased oxidative stress (Bartalena et al, 2003) and prior radioactive iodine (RAI) therapy has been associated with new onset or worsening of TED (Bartalena et al, 2020; Chin et al, 2020).
Main existing treatment options	There is currently no medicinal product specifically approved in the European Union (EU) for the treatment of TED. Teprotumumab was approved for the treatment of TED by the US Food and Drug Administration (FDA) in January 2020. According to the 2021 EUGOGO clinical practice guidelines for the medical management of TED, the treatment decisions should be based on the assessment of clinical activity and severity of TED (Bartalena et al, 2021).

Table 2. Summary of Epidemiology of Thyroid Eye Disease

Main existing treatment options (continued)	Clinical practice guidelines currently recommend a combination of intravenous (IV) methylprednisolone and mycophenolate sodium as standard of care for moderate to severe and active TED. Second line treatments for moderate to severe and active TED include: • The second course of IV methylprednisolone (7.5 g) subsequent to careful ophthalmic and biochemical evaluation • Oral prednisone/prednisolone combined with either cyclosporine or azathioprine • Orbital radiotherapy combined with oral or IV glucocorticoids • Teprotumumab • Rituximab • Tocilizumab
Natural history of the indicated condition in the untreated population, including mortality and morbidity	Without treatment, TED consists of an initial active phase with orbital inflammation escalating over months, followed by a static, inactive phase after 12 to 18 months, where proptosis and ocular motility restriction improve but may persist (Khong and McNab, 2021; Hwang and Eftekhari, 2020). Mild TED involves an initial inflammatory period underpinned by ongoing orbital activation of autoimmune reactions (active phase). Thyroid eye disease then stabilizes when inflammation starts to subside (plateau or static phase) and progressively remits following burning out of inflammation (inactive phase), possibly associated with fibrotic changes. Extraocular muscle enlargement seems to occur earlier than orbital fat expansion. Studies have shown that mild/minimal TED rarely progresses to more severe forms, whereas stabilization and remission are frequent (Bartalena and Tanda, 2022). Patients with moderate to severe TED may have the same natural history as patients with mild TED (Bartalena and Tanda, 2022). There may be slow improvement after months to years of inactive, plateaued disease. Nevertheless, most patients with moderate to severe TED do not achieve complete recovery back to normal, with proptosis being the last likely manifestation to resolve (Rashad et al, 2022). The most common ocular sign of TED is upper eyelid retraction, occurring in 90% of the patients, followed by proptosis and ocular motility restriction. Thyroid eye disease can be debilitating as it may lead to diplopia, ocular hypertension, optic nerve damage and glaucoma (Eshraghi et al, 2021; Chin et al, 2020; Muñoz-Ortiz et al, 2020). Thyroid eye disease was also found associated with increased psychosocial morbidity. Thyroid eye disease clinical manifestations, such as disturbances in visual function, physical discomfort, and facial disfigurement, can result in significant psychological morbidity that can be detrimental to a patient's quality of life. Visual impairment can have a significant impact on functional status, resulting in limitations of daily activities such as work productivity. The facial disfigurement caused by TED negatively influences facial expression, communication, self-perception, and social interactions, leading to an increased risk of psychological disturbances such as anxiety and depression. Additionally, the treatment options such as high-dose glucocorticoids, retrobulbar irradiation, or surgery, may cause severe side effects that may inflict physical and psychological morbidity and thereby increase mortality (Kahaly et al, 2005).

Table 2. Summary of Epidemiology of Thyroid Eye Disease

Natural history of the indicated condition in the untreated population, including mortality and morbidity (continued)	In a large-scale nationwide Danish cohort study comprising 3965 patients with TED, a 23% increased mortality was found compared with an age- and gender-matched control population and an inverse relationship between mortality and age (Schwensen et al, 2017).
Important comorbidities	Important comorbidities include Graves' disease, diabetes mellitus type 1 and 2, Hashimoto's thyroiditis (Eshraghi et al, 2021).

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Part II: Module SII - Nonclinical Part of the Safety Specification

Table 3. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Toxicity		
• Key issues identified from acute or repeat-dose toxicity studies	Teprotumumab-associated effects identified in repeat-dose toxicology studies were limited to reversible thymic atrophy (with correlating microscopic thymic lymphoid depletion), decreased alkaline phosphatase and minimally lower erythrocyte mass. These findings were reversible and were either limited in magnitude or had no impact on the animals' overall health	Based on current clinical experience and data, these findings are not expected to translate to humans.
• Reproductive toxicity	Teprotumumab was intravenously administered to pregnant cynomolgus monkeys once weekly from gestation day 20 to 142 at a 75 mg/kg dose (8.3-fold the maximum recommended human dose, based on the AUC). Teprotumumab showed evidence of embryo-fetal toxicity that included smaller overall size (for their gestational age) and multiple external and skeletal abnormalities of the head, including misshapen cranium, micrognathia, and ossification abnormalities of multiple bones and teeth. The effects observed in cynomolgus monkeys were consistent with the pharmacology of teprotumumab as an inhibitor of IGF signalling pathways, which are known to be involved in regulation of fetal growth and development. A formal fertility study with teprotumumab has not been performed. Repeat-dose toxicology studies in cynomolgus monkeys with weekly teprotumumab administration of up to 39-weeks did not reveal any histopathological changes in male or female reproductive organs.	Exposure to teprotumumab during pregnancy may cause harm to the fetus. Teprotumumab induced developmental toxicity in animals. Thus, women of childbearing potential should use highly effective contraception prior to, while receiving teprotumumab, and for 6 months after the last administration. It is not known if teprotumumab is excreted in human milk. As a precautionary measure, teprotumumab should not be used during breastfeeding. Embryofetal toxicity is included as an important potential risk (Table 18).

Abbreviations are defined on the last page of this table.

Table 3. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Toxicity (continued)		
• Developmental toxicity	Teprotumumab was evaluated in a 13-week juvenile monkey study at doses of 3, 15, and 75 mg/kg/week IV. Adverse findings were limited to decreased body weight gain (all dose levels) and decreased bone mass (bone mineral content and density) in males (all dose levels) and narrower bones with thinner cortices in males (all dose levels) and females (75 mg/kg/week); these findings were generally reversible following a 13-week recovery period. Bone diameter was consistently lower for all exposed males and females, suggesting an inhibition of periosteal expansion that is consistent with IGF-1 effects on periosteal growth and expansion. Other key treatment-related findings were similar to those observed in adult animal repeat-dose studies and were not considered adverse due to the limited magnitude of the change or lack of adverse physiological effect. These findings were decreased alkaline phosphate, minimally lower erythrocyte mass, and smaller thymus size that correlated to microscopic lymphocyte depletion in the thymus. The aforementioned findings were either fully reversed or showing signs of reversibility (ie, partial reversal) at the end of the 13-week recovery period.	Teprotumumab should not be used in children from birth to adolescence before growth is complete as safety has not been demonstrated and adverse bone effects are present in exposed juvenile animals.

AUC = area under the curve; IGF = insulin-like growth factor; IGF-1 = insulin-like growth factor-1; IV = intravenously

Part II: Module SIII - Clinical Trial Exposure

Table 4. Total Subject Exposure to Teprotumumab in Clinical Trials by Indication and Duration
Safety Analysis Set

	Exposure to Teprotumumab by Duration						
Indication	< 1 Month n (subj-yrs)	1 - < 3 Months n (subj-yrs)	3 - < 6 Months n (subj-yrs)	6 - < 9 Months n (subj-yrs)	9 - < 12 Months n (subj-yrs)	≥ 12 Months n (subj-yrs)	Total n (subj-yrs)
Thyroid Eye Disease	6 (0.3)	3 (0.5)	209 (84.0)	3 (1.8)	25 (20.4)	0 (0.0)	246 (106.8)
Total	6 (0.3)	3 (0.5)	209 (84.0)	3 (1.8)	25 (20.4)	0 (0.0)	246 (106.8)

n = number of subjects exposed to teprotumumab; subj-yrs = total subject-years exposed to teprotumumab

Exposure duration (in days) = last dosing date - first dosing date +1. If subjects received teprotumumab more than 1 course in multiple phases or an open-label treatment period in the same or different studies, individual exposure durations are added to get a total duration for those subjects.

Total subject-years exposed to teprotumumab = (sum of the total duration [in days] for individual subjects)/365.25.

Note: Data are from completed studies, ongoing open-label studies, and unblinded studies that had early or interim analyses completed as of 20 January 2024 in subjects with moderate to severe thyroid eye disease (TED01RV, HZNP-TEP-301 [OPTIC], HZNP-TEP-302 [OPTIC-X], HZNP-TEP-303 [OPTIC J], HZNP-TEP-401 and HZNP-TEP-403). Study HZNP-TEP-102 was conducted in healthy volunteers and, accordingly, it is not included for the purpose of the clinical trial exposure tables. A study is considered completed if a final clinical study report is available. Safety analysis set includes subjects who received at least 1 dose of investigational product.

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Table 5. Total Subject Exposure to Teprotumumab in Clinical Trials by Age Group and Gender
Safety Analysis Set

Indication/Gender	Adults (18 to 64 years) n (subj-yrs)	Elderly Patients (≥ 65 years) n (subj-yrs)	Total n (subj-yrs)
Male			
Thyroid Eye Disease	57 (24.4)	13 (5.5)	70 (29.9)
Total	57 (24.4)	13 (5.5)	70 (29.9)
Female			
Thyroid Eye Disease	155 (67.0)	21 (9.9)	176 (76.9)
Total	155 (67.0)	21 (9.9)	176 (76.9)

n = number of subjects exposed to teprotumumab; subj-yrs = total subject-years exposed to teprotumumab

Exposure duration (in days) = last dosing date - first dosing date +1. If subjects received teprotumumab more than 1 course in multiple phases or an open-label treatment period in the same or different studies, individual exposure durations are added to get a total duration for those subjects.

Total subject-years exposed to teprotumumab = (sum of the total duration [in days] for individual subjects)/365.25.

Note: Data are from completed studies, ongoing open-label studies, and unblinded studies that had early or interim analyses completed as of 20 January 2024 in subjects with moderate to severe thyroid eye disease (TED01RV, HZNP-TEP-301 [OPTIC], HZNP-TEP-302 [OPTIC-X], HZNP-TEP-303 [OPTIC J], HZNP-TEP-401 and HZNP-TEP-403). Study HZNP-TEP-102 was conducted in healthy volunteers and, accordingly, it is not included for the purpose of the clinical trial exposure tables. Safety analysis set includes subjects who received at least 1 dose of investigational product.

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Table 6. Total Subject Exposure to Teprotumumab in Clinical Trials by Product and Race
Safety Analysis Set

	White n (subj-yrs)	Black or African American n (subj-yrs)	Asian n (subj-yrs)	Native Hawaiian or Other Pacific Islander n (subj-yrs)	Other n (subj-yrs)	Missing/ Unknown n (subj-yrs)	Total n (subj-yrs)
Thyroid Eye Disease	154 (66.2)	20 (9.9)	64 (27.6)	1 (0.4)	7 (2.8)	0 (0.0)	246 (106.8)
Total	154 (66.2)	20 (9.9)	64 (27.6)	1 (0.4)	7 (2.8)	0 (0.0)	246 (106.8)

n = number of subjects exposed to teprotumumab; subj-yrs = total subject-years exposed to teprotumumab

Exposure duration (in days) = last dosing date - first dosing date +1. If subjects received teprotumumab more than 1 course in multiple phases or an open-label treatment period in the same or different studies, individual exposure durations are added to get a total duration for those subjects.

Total subject-years exposed to teprotumumab = (sum of the total duration [in days] for individual subjects)/365.25.

Note: Data are from completed studies, ongoing open-label studies, and unblinded studies that had early or interim analyses completed as of 20 January 2024 in subjects with moderate to severe thyroid eye disease (TED01RV, HZNP-TEP-301 [OPTIC], HZNP-TEP-302 [OPTIC-X], HZNP-TEP-303 [OPTIC J], HZNP-TEP-401 and HZNP-TEP-403). Study HZNP-TEP-102 was conducted in healthy volunteers and, accordingly, it is not included for the purpose of the clinical trial exposure tables. Safety analysis set includes subjects who received at least 1 dose of investigational product.

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Table 7. Total Subject Exposure to Teprotumumab in Clinical Trials by Product and Ethnic Group
Safety Analysis Set

	Hispanic/Latino n (subj-yrs)	Non-Hispanic/Latino n (subj-yrs)	Missing/ Unknown n (subj-yrs)	Total n (subj-yrs)
Thyroid Eye Disease	14 (5.6)	232 (101.2)	0 (0.0)	246 (106.8)
Total	14 (5.6)	232 (101.2)	0 (0.0)	246 (106.8)

n = number of subjects exposed to teprotumumab; subj-yrs = total subject-years exposed to teprotumumab

Exposure duration (in days) = last dosing date - first dosing date +1. If subjects received teprotumumab more than 1 course in multiple phases or an open-label treatment period in the same or different studies, individual exposure durations are added to get a total duration for those subjects.

Total subject-years exposed to teprotumumab = (sum of the total duration [in days] for individual subjects)/365.25.

Note: Data are from completed studies, ongoing open-label studies and unblinded studies that had early or interim analyses completed as of 20 January 2024 in subjects with moderate to severe thyroid eye disease (TED01RV, HZNP-TEP-301 [OPTIC], HZNP-TEP-302 [OPTIC-X], HZNP-TEP-303 [OPTIC J], HZNP-TEP-401 and HZNP-TEP-403). Study HZNP-TEP-102 was conducted in healthy volunteers and, accordingly, it is not included for the purpose of the clinical trial exposure tables. Safety analysis set includes subjects who received at least 1 dose of investigational product.

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Part II: Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Table 8. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Patients with known hypersensitivity to any of the components of teprotumumab or prior hypersensitivity reactions to monoclonal antibodies	History of hypersensitivity is a routine exclusion criterion in development studies.	No	Infusion-related reaction, including hypersensitivity, is a labelled event for teprotumumab and is a contraindication in the SmPC.
Patients with decreased best corrected visual acuity due to optic neuropathy as defined by a decrease in vision of 2 lines on the Snellen chart, new visual field defect, or color defect secondary to optic nerve involvement within the last 6 months	Patients with significant optic neuropathy were excluded as this can impact the assessment of drug efficacy and safety.	No	There is no evidence that teprotumumab has a different safety profile in this population.
Patients with corneal decompensation unresponsive to medical management	Patients with significant corneal decompensation were excluded as this can impact assessment of drug safety and efficacy	No	There is no evidence that teprotumumab has a different safety profile in this population.
Patients using any concomitant corticosteroid (IV or oral) with a cumulative dose equivalent to ≥ 1 g of methylprednisolone for the treatment of TED	Corticosteroids are known to exert anti-inflammatory and immunosuppressive actions and were prohibited to enable accurate assessment of teprotumumab efficacy.	No	No impact on safety of teprotumumab is anticipated from concurrent corticosteroid use.
Patients with previous orbital irradiation or surgery for TED	Orbital radiotherapy and surgical intervention for TED are known to mitigate the disease manifestations and therefore could confound efficacy.	No	There is no evidence that teprotumumab has a different safety profile in this population.

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Abbreviations are defined on the last page of this table.

Table 8. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Patients previously treated with rituximab within 12 months or tocilizumab within 6 months. Use of any other non-steroid immunosuppressive agent in the previous 3 months	Use of rituximab, tocilizumab, and any other non-steroid immunosuppressive agent are known to impact the immune system; the drugs were prohibited to enable accurate assessment of teprotumumab efficacy and safety.	No	There is no evidence that teprotumumab has a different safety profile in the combined administration of immunosuppressive agents.
Patients with a malignant condition in the past 12 months (with the exception of successfully treated basal cell carcinoma of the skin)	Morbid malignancy may have a significant impact on survival and the management strategy chosen for cancer; thus, these patients were excluded due to potential impact on safety assessments.	No	There is no evidence that teprotumumab has a different safety profile in this population.
Use during pregnancy and lactation	The safety of the drug in this population is unknown. However, based on the teratogenic effects of teprotumumab noted in animal reproduction studies and its mechanism of action, teprotumumab may cause fetal harm when administered to a pregnant woman.	No	As per SmPC, teprotumumab is contraindicated in pregnancy and appropriate forms of contraception should be implemented prior to initiation, during treatment, and for 6 months following the last dose of teprotumumab. It is not known if teprotumumab is excreted in human milk, the effects on the breastfed infant or the effects on milk production. The SmPC recommends that teprotumumab should not be used during breastfeeding. Embryofetal toxicity is included as an important potential risk (Table 18).

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IV = intravenous; SmPC = Summary of Product Characteristics; TED = thyroid eye disease

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programs

Table 9. SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	Not included in the clinical development program
Patients with relevant comorbidities	
Patients with hepatic impairment	Not included in the clinical development program
Patients with renal impairment	Not included in the clinical development program
Patients with cardiovascular impairment	Not included in the clinical development program
Immunocompromised patients	Not included in the clinical development program
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
Population with relevant different ethnic origin	Table 6 and Table 7 provide exposure by race and ethnic origin of participants included in the clinical development program.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program
Other	Not included in the clinical development program

Part II: Module SV - Postauthorization Experience

SV.1 Postauthorization Exposure

SV.1.1 Method Used to Calculate Exposure

Amgen's estimates of postmarketing patient exposure are in part based on unit sales data (eg, vials or syringes), and in part on observed drug utilization parameters. Worldwide unit sales are recorded monthly by country and are converted to a monthly estimate of person count (when feasible) or person-time using region- and product-specific utilization parameters and algorithms. These parameters include the average number of mg per administration, average length of treatment, days between administrations, patient turnover rates, market penetration rates, and average revenue per patient. These drug utilization parameters can change over time to best represent the current patient and market experience.

The cumulative number of patients exposed (or patient-years of exposure) to teprotumumab through commercial distribution is shown in Table 10 below.

SV.1.2 Exposure

Table 10. Estimated Number of Patient-years of Exposure to Teprotumumab, by Region in the Postmarketing Setting

Cumulative[a] Number of Patient-years of Exposure			
US	Brazil	Saudi Arabia	Global
10 556	3	7	10 565

US = United States
Note: Data based on sales figures.
[a] Cumulatively through 20 July 2024.
Note: Numbers may not add to the total due to rounding.

An Early Access Program is ongoing in countries where teprotumumab has not yet been granted marketing authorization. Cumulatively, since the program started in June 2021, 60 patient-years of exposure were accrued through this program.

Postauthorization Use From Business Partners

Not applicable.

Part II: Module SVI - Additional EU Requirements for the Safety Specification

SVI.1 Potential for Misuse for Illegal Purposes

No evidence to suggest a potential for drug abuse or misuse has been observed.

Part II: Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table 11. Reasons for Not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP

Reasons for Not Including an Identified or Potential Risk in the List of Safety Concerns	List of Risks
Known risks that do not impact the risk-benefit profile: Teprotumumab should not be used in children from birth to adolescence before growth is complete as safety and effectiveness have not been established in this population. Thyroid eye disease occurs very rarely in pediatric patients, and it is typically mild. Therefore, it is unlikely that it will be used in this population.	Growth and developmental effects
Risks with minimal clinical impact on patients (in relation to the severity of the indication treated): Most of the events were non-serious and mild to moderate in severity. These events are included in the EU SmPC as adverse reactions and the clinical impact on the patient is considered to be low in relation to the severity of the indication treated. Additional pharmacovigilance and additional risk minimization activities are not proposed for these risks.	Infection Muscle spasms Alopecia Fatigue Nausea Headache Dysgeusia Weight decreased Menstrual disorders

EU = European Union; SmPC = Summary of Product Characteristics

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table 12. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Safety Concern	Risk-benefit Impact
Important Identified Risks	
Hyperglycemia	Teprotumumab leads to IGF-1R blockade and therefore could cause a loss of feedback inhibition of the growth hormone and IGF-1 axis leading to greater glucose and insulin levels (Pollak, 2012). This risk is considered important as uncontrolled hyperglycemia can cause serious acute complications (eg, diabetic ketoacidosis [DKA] and hyperosmolar hyperglycemic state [HHS]).
Exacerbation of inflammatory bowel disease (IBD)	Although the etiology of IBD remains unknown, patients with active disease present with reduced serum and gastrointestinal (GI) levels of IGF-1. The decreased availability of IGF-1 induced inhibition of IGF-1R by teprotumumab may mimic the conditions that can be found in patients with IBD and can lead to GI symptoms and signs (Safo and Silkiss, 2021). This risk is considered important due to the potential to exacerbate the disease that may lead to discontinuation of the treatment and may require intensive medical interventions.
Infusion-related reactions	Infusion reactions are anticipated with infusion of foreign proteins such as mAbs (Teo et al, 2021; Scherer et al, 2010). This risk is considered important as severe infusion-related reactions or even life-threatening anaphylactic reactions can occur with monoclonal antibody (mAb) administration.
Hearing impairment	IGF-1 is known to be crucial to the development of the inner ear, as well as the maintenance and protective mechanisms for hearing. Genetic IGF-1 deficiency has been associated with devastating hearing loss in human and animal studies. Though a causal mechanism is not yet determined, teprotumumab mediated IGF-1R inhibition may still be deemed a risk factor for hearing loss, due to the strong relationship between IGF-1 and otologic health (Chern et al, 2021; Yu et al, 2021). This risk is considered important as teprotumumab may cause severe hearing impairment, which in some cases may be permanent.

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Abbreviations are defined on the last page of this table.

Table 12. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Safety Concern	Risk-benefit Impact
Important Potential Risks	
New onset IBD	It is difficult to distinguish new onset IBD and exacerbation of pre-existing IBD based on clinical manifestations. In addition, the possible biological plausibility that teprotumumab may cause IBD worsening (see above) is also applicable to new onset IBD. At this time, there have been no safety reports of new onset IBD in trials. As such, new onset IBD is considered an important potential risk. This risk is considered important due to the potential to trigger IBD and the need for intensive medical care.
Embryofetal toxicity	No human developmental and reproductive studies were conducted with teprotumumab. Studies in animals have shown developmental toxicity. For these reasons, exposure to teprotumumab during pregnancy may cause harm to the fetus. Therefore, teprotumumab is contraindicated in pregnant women in the SmPC and contraception prior to initiation, during treatment, and for 6 months after last administration is recommended. Based on embryofetal toxicity reported in the nonclinical studies and contraindication of the product in pregnancy (SmPC Sections 4.3 and 4.6), embryofetal toxicity is included as an important potential risk.
Missing Information	
Safety in retreated patients	Relapse of TED has occurred in some subjects after completing treatment with teprotumumab. Retreatment is expected to be needed in clinical practice. Some subjects were treated with a second course of teprotumumab in clinical studies and teprotumumab was well tolerated in these subjects. The data available are not considered sufficient to fully determine the safety profile after re-treatment.

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DKA = diabetic ketoacidosis; GI = gastrointestinal; HHS = hyperosmolar hyperglycemic state; IBD = inflammatory bowel disease; IGF-1 = insulin-like growth factor-1; IGF-1R = insulin-like growth factor-1 receptor; mAb = monoclonal antibody; RMP = risk management plan; SmPC = Summary of Product Characteristics; TED = thyroid eye disease

SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

Not applicable, as this is an initial marketing authorization application.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Table 13. Important Identified Risk: Hyperglycemia

Potential mechanisms	Teprotumumab leads to IGF-1R blockade and therefore could cause a loss of feedback inhibition of the growth hormone and IGF-1 axis leading to greater glucose and insulin levels (Pollak, 2012).
Evidence source(s) and strength of evidence	The risk was identified in randomized controlled clinical trials and further confirmed from postmarketing data.
Characterization of the risk	
Frequency	In the pooled clinical studies (TED01RV, HZNP-TEP-301 [OPTIC], HZNP-TEP-303 [OPTIC J], and HZNP-TEP-403 n = 152), hyperglycemia events were observed in 20 of 152 subjects (13.2%) in the teprotumumab group.
Severity	**Clinical Trials:** One patient developed DKA. All events of hyperglycemia for participants in the teprotumumab group during study were mild to moderate in severity. **Postmarketing**: Cases of hyperosmolar hyperglycemic state have also been observed in patients with prediabetes and diabetes. Hyperglycemia in most patients was reported as mild to moderate in severity.
Reversibility	Hyperglycemia may persist after stopping teprotumumab especially in those with diabetes mellitus or prediabetes.
Long-term outcomes	No data on long term outcomes are available.
Impact on quality of life	Uncontrolled hyperglycemia can cause serious diabetic complications such as DKA and HHS.
Risk groups or risk factors	Risk groups: • Patients with pre-existing diabetes mellitus. • Patients with impaired glucose tolerance (Teo et al, 2021).
Preventability	In line with the SmPC Section 4.4, it is recommended that blood glucose and symptoms of hyperglycemia are monitored closely in patients prior to infusion and while on treatment with teprotumumab. Patients with hyperglycemia or pre-existing diabetes should be under appropriate glycemic control before and while receiving teprotumumab. Blood glucose monitoring is recommended for 6 months after completion of treatment with teprotumumab.

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 13. Important Identified Risk: Hyperglycemia

Impact on the risk-benefit balance of the product	The risk-benefit balance with respect to hyperglycemia is considered positive. In clinical trials, the events of hyperglycemia with teprotumumab treatment were mild or moderate in severity and mostly resolved, either on or off treatment. Furthermore, it is anticipated that the important identified risk of hyperglycemia can be adequately managed by the risk minimization measures in the EU SmPC.
Public health impact	Due to the relatively small number of patients exposed to teprotumumab, there would be only a few patients per year that would be expected to experience hyperglycemia and considering the possibility to identify patients predisposed to the risk the public health impact is considered low.

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DKA = diabetic ketoacidosis; EU = European Union; HHS = hyperosmolar hyperglycemic state; IGF-1 = insulin-like growth factor-1; IGF-1R = insulin-like growth factor-1 receptor; SmPC = Summary of Product Characteristics

Table 14. Important Identified Risk: Exacerbation of Inflammatory Bowel Disease

Potential mechanisms	Although the etiology of IBD remains unknown, patients with active disease present with reduced serum and GI levels of IGF-1. The decreased availability of IGF-1 induced inhibition of IGF-1R by teprotumumab may mimic the conditions that can be found in patients with IBD and can lead to GI symptoms and signs (Safo and Silkiss, 2021).
Evidence source(s) and strength of evidence	The risk was identified in randomized controlled clinical trials.
Characterization of the risk	
Frequency	In the pooled clinical studies (TED01RV, HZNP-TEP-301 [OPTIC], HZNP-TEP-303 [OPTIC J], and HZNP-TEP-403, n = 152) exacerbation of inflammatory bowel disease events were observed in 1 of 152 subjects (0.7%).
Severity	The reported case of exacerbation of IBD was severe and subject recovered with sequelae.
Reversibility	No data on reversibility are available
Long-term outcomes	There is no specific data regarding the long-term outcomes of the IBD following teprotumumab administration, however it is acknowledged that the long-term effects of the IBD may involve chronic inflammation of the GI tract.
Impact on quality of life	The chronic nature and severity of symptoms in IBD cause stress, anxiety and depression which are associated with lower quality of life for patients with IBD (Mitropoulou et al, 2022).
Risk groups or risk factors	Risk groups: • Patients with known history of IBD (ulcerative colitis or Crohn's disease). • Patients with family history of IBD (Ashraf et al, 2021)
Preventability	In line with the SmPC Section 4.4, patients with IBD should be monitored for flare of disease. If exacerbation of inflammatory bowel disease is suspected, teprotumumab should be discontinued.

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 14. Important Identified Risk: Exacerbation of Inflammatory Bowel Disease

Impact on the risk-benefit balance of the product	The event reported was severe and led to discontinuation of trial drug in TED trials. However, it is anticipated that the important identified risk of IBD can be adequately managed with the risk minimization measures described in the SmPC including recommendation to monitor patients with IBD for flare of disease and discontinuation of teprotumumab if exacerbation of inflammatory bowel disease is suspected. The risk-benefit balance with respect to exacerbation of IBD is considered positive.
Public health impact	Risk of exacerbation of IBD is low especially in subjects without family history or genetic predisposition to IBD. Intended population of teprotumumab (moderate to severe TED) is small (estimated 1.61 per 100 000 people per year). Therefore public health impact is low.

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GI = gastrointestinal; IBD = inflammatory bowel disease; IGF-1 = insulin-like growth factor-1; IGF-1R = insulin-like growth factor-1 receptor; SmPC = Summary of Product Characteristics; TED = thyroid eye disease

Table 15. Important Identified Risk: Infusion-related Reactions

Potential mechanisms	The biologic mechanism of infusion-related reactions (IRRs) is not well understood; however, as with all therapeutic proteins, administration of teprotumumab might result in IRRs.
Evidence source(s) and strength of evidence	The risk was identified in randomized controlled clinical trials and further confirmed from postmarketing data.
Characterization of the risk	
Frequency	In the pooled clinical studies (TED01RV, HZNP-TEP-301 [OPTIC], HZNP-TEP-303 [OPTIC J], and HZNP-TEP-403, n = 152) IRR events were observed in 8 of 152 subjects (5.3%).
Severity	Reported IRR events are usually mild or moderate in severity. There were no severe, life-threatening, or fatal events.
Reversibility	Generally, IRR events associated with teprotumumab have been self-limited, mostly resolved within couple of hours and there was no recurrence with subsequent infusions.
Long-term outcomes	No specific data are available for teprotumumab.
Impact on quality of life	Severe IRRs or even life-threatening anaphylactic reaction can occur with mAb IV administration.
Risk groups or risk factors	Risk group: • Patients with known history of hypersensitivity and IRRs
Preventability	Infusion-related reactions are included in Sections 4.2, 4.4, and 4.8 of the SmPC. The risk of IRRs can be prevented with premedication comprising a corticosteroid, an antihistamine, an antipyretic, and/or administering all subsequent infusions at a slower infusion rate.
Impact on the risk-benefit balance of the product	The risk-benefit with respect to IRRs is considered positive. Most reported events were mild or moderate in severity. It is anticipated that the important identified risk of IRR can be adequately managed by the routine risk minimization measures in the SmPC.
Public health impact	Intended population of teprotumumab (moderate to severe TED) is small (estimated 1.61 per 100 000 people per year). Frequency of IRRs observed with teprotumumab is low and severity is typically mild or moderate, and non-serious. Therefore, the public health impact of this risk is expected to be low.

CDS = core data sheet; mAb = monoclonal antibody; IRR = infusion-related reaction; IV = intravenous; SmPC = Summary of Product Characteristics; TED = thyroid eye disease

Table 16. Important Identified Risk: Hearing Impairment

Potential mechanisms	Insulin-like growth factor-1 is known to be crucial to the development of the inner ear, as well as the maintenance and protective mechanisms for hearing. Genetic IGF-1 deficiency has been associated with devastating hearing loss in human and animal studies. Though a causal mechanism is not yet determined, teprotumumab mediated IGF-1R inhibition may still be deemed a risk factor for hearing loss, due to the strong relationship between IGF-1 and otologic health (Chern et al, 2021; Yu et al, 2021).
Evidence source(s) and strength of evidence	Overall, during the development program, hearing impairment occurred at a higher incidence among participants in the teprotumumab group compared to the placebo group. In the postmarketing setting, cases of hearing impairment have been reported, some of which have been severe.
Characterization of the risk	
Frequency	In the pooled clinical studies (TED01RV, HZNP-TEP-301 [OPTIC], HZNP-TEP-303 [OPTIC J], and HZNP-TEP-403 n = 152), hearing impairment events including hearing loss (deafness, including sensorineural deafness, eustachian tube dysfunction, eustachian tube patulous, hyperacusis, hypoacusis, autophony, tinnitus, and tympanic membrane disorder) were observed in 21 of 152 subjects (13.8%).
Severity	The majority of hearing impairment events in clinical trials were mild to moderate in severity and did not lead to discontinuation of trial drug.
Reversibility	Hearing impairment may resolve following completion of standard course of treatment. However, teprotumumab may cause severe hearing impairment including hearing loss, which in some cases may be permanent.
Long-term outcomes	In some cases, hearing impairment events were persistent. Subjects without risk factors and baseline hearing impairment typically returned to normal hearing.
Impact on quality of life	Teprotumumab may cause severe hearing impairment, including permanent hearing loss.
Risk groups or risk factors	There are no data on risk factors or risk groups for patients with TED treated with teprotumumab.

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 16. Important Identified Risk: Hearing Impairment

Preventability	No preventive measures are known. However, Section 4.4 of the SmPC has the following recommendations. Patients should be advised to report symptoms of altered hearing promptly to their healthcare professional. The benefit-risk of treatment should be considered in patients with pre-existing hearing impairment. Patients' 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 hearing in these patients for up to 6 months after completion of treatment. Teprotumumab should be discontinued in patients experiencing hearing loss that requires intervention, limits their ability to self-care, or is considered profound. 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. Caution is needed when co-administering teprotumumab in patients who are receiving concomitant therapies known to cause ototoxicity (eg, aminoglycosides, vancomycin, platinum-containing chemotherapeutic medicinal products, loop diuretics) due to the potential risk of additive effects on hearing impairment. A Healthcare Professional Guide and Patient Guide are provided (see Part V.2).
Impact on the risk-benefit balance of the product	The risk-benefit balance of teprotumumab in the indication of TED remains positive as teprotumumab demonstrated efficacy compared to placebo and hearing impairment events are generally mild to moderate in intensity and reversible following completion of treatment. For patients who experience severe hearing impairment during the treatment, the benefit-risk of continuing treatment with teprotumumab should be considered. The impact of hearing impairment can be minimized through product labeling and use of the Healthcare Professional Guide and Patient Guide.
Public health impact	Intended population of teprotumumab (moderate to severe TED) is small (estimated 1.61 per 100 000 people per year). The risk of hearing impairment with teprotumumab treatment is considered to be low. Therefore, the public health impact is considered low.

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IGF-1 = insulin-like growth factor-1; IGF-1R = insulin-like growth factor-1 receptor; SmPC = Summary of Product Characteristics; TED = thyroid eye disease

Table 17. Important Potential Risk: New Onset Inflammatory Bowel Disease

Potential mechanisms	Although the etiology of IBD remains unknown, patients with active disease present with reduced serum and GI levels of IGF-1. The decreased availability of IGF-1 induced inhibition of IGF-1R by teprotumumab may mimic the conditions that can be found in patients with IBD and can lead to GI symptoms and signs (Safo and Silkiss, 2021).
Evidence source(s) and strength of evidence	It is difficult to distinguish new onset IBD and exacerbation of pre-existing IBD based on clinical manifestations. In addition, the possible biological plausibility that teprotumumab may cause IBD worsening (see above) is also applicable to new onset IBD. At this time, there are no safety reports of new onset IBD in clinical trials. There were 2 solicited cases reporting new onset IBD for which medical history, physician confirmation, or time to onset is not available. As such, new onset IBD is considered an important potential risk.
Characterization of the risk	
Frequency	Not applicable.
Severity	Not applicable - no cases have been detected.
Reversibility	No data on reversibility are available.
Long-term outcomes	There is no specific data regarding the long-term outcomes of IBD following teprotumumab administration, however it is acknowledged that the long-term effects of IBD may involve chronic inflammation of the GI tract.
Impact on quality of life	The chronic nature and severity of symptoms in IBD cause stress, anxiety and depression which are associated with lower quality of life for patients with IBD (Mitropoulou et al, 2022)
Risk groups or risk factors	Risk groups: • Patients with family history of IBD (Ashraf et al, 2021).
Preventability	No preventive measures are known.
Impact on the risk-benefit balance of the product	The risk-benefit with respect to new onset IBD is considered positive.
Public health impact	New onset IBD is a theoretical risk. Public health impact is not known.

GI = gastrointestinal; IBD = inflammatory bowel disease; IGF-1 = insulin-like growth factor-1; IGF-1R = insulin-like growth factor-1 receptor

Table 18. Important Potential Risk: Embryofetal Toxicity

Potential mechanisms	IGF-1 is an important mediator of normal and abnormal growth, and the IGF-1 pathway plays a critical role in both intrauterine and postnatal development or growth. In an animal study, maternal exposure to teprotumumab was associated with decreased weight and skeletal abnormalities. Based on mechanism of action of IGF-1R inhibition, exposure to teprotumumab may cause fetal harm (Bowman et al, 2010).
Evidence source(s) and strength of evidence	The source of information is nonclinical study (animal) data and its mechanism of action as IGF-1R inhibitor.
Characterization of the risk	
Frequency	The use of teprotumumab in pregnant or lactating women has not been evaluated in clinical trials. Based on the animal reproduction studies on the teratogenic effects of teprotumumab and its mechanism of action, teprotumumab may cause fetal harm when administered to a pregnant woman. In an abridged pilot embryofetal development study, 7 pregnant cynomolgus monkeys were dosed intravenously of teprotumumab, 75 mg/kg (8.3-fold the maximum recommended human dose based on area under the curve) once weekly from 20th day of gestation through the end of gestation. Results showed that the incidence of abortion was higher for the teprotumumab treated group compared to the control group. Teprotumumab exposure may lead to an increase in fetal loss. Therefore, teprotumumab should not be used during pregnancy. Cumulatively up to 20 July 2024, 10 postmarketing cases of pregnancy have been reported, of which 2 reported spontaneous abortion. In 1 case of spontaneous abortion, the patient became pregnant 1 year after finishing teprotumumab treatment and had a miscarriage 3 months later. The other case reported 2 miscarriages since starting treatment but no information on medical history, concomitant medications, or laboratory data were provided. The outcome of the pregnancies was unknown for the remaining 8 cases.
Severity	No pregnancies were reported in the clinical trials. All postmarketing pregnancy events were non-serious except for the 2 events of spontaneous abortion, which were both serious. Outcomes were unknown for all events.
Reversibility	No data on reversibility are available.
Long-term outcomes	No data regarding the long-term outcomes are available.
Impact on quality of life	No data regarding the impact on quality of life are available.

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 18. Important Potential Risk: Embryofetal Toxicity

Risk groups or risk factors	There are no known risk factors for embryofetal toxicity in patients treated with teprotumumab. Risk groups: • Women planning to become pregnant; • Women of childbearing potential not using effective birth control measures; • Pregnant women (Douglas et al, 2021).
Preventability	In line with the teprotumumab SmPC, teprotumumab should not be used during pregnancy. Effective contraceptive (methods that result in less than 1% pregnancy rates) should be used prior to initiation, during the treatment, and for 6 months after treatment. In addition, a Healthcare Professional Guide and Patient Guide are provided (see Part V.2).
Impact on the risk-benefit balance of the product	The TED population is less likely to include pregnant women as the median age at onset of TED is 50 years and predominant prevalence is observed in the 50 to 59 years age group. Literature indicates that the prevalence of TED in pregnancy is rare. Graves' disease and hyperthyroidism, both precursors to TED, are known causes of human subfertility and infertility; an estimated ~0.5% of women becoming pregnant have Graves' disease, ~0.2% are treated during pregnancy, and the risk of developing Graves' disease during pregnancy is very low (~0.05%) (Davies et al, 2020). The important potential risk of embryofetal toxicity is not considered to meaningfully impact the benefit-risk profile of teprotumumab considering the targeted population and indication. The impact of embryofetal toxicity can be minimized through product labeling and use of the Healthcare Professional Guide and Patient Guide.
Public health impact	Adequate well-controlled studies are not available in human pregnancy. However, taking into consideration the preventive measures in place, the potential risk of embryofetal toxicity and the public health impact is considered low.

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IGF-1 = insulin-like growth factor-1; IGF-1R = insulin-like growth factor-1 receptor; SmPC = Summary of Product Characteristics; TED = thyroid eye disease

SVII.3.2 Presentation of the Missing Information

Table 19. Missing Information: Safety in Retreated Patients

Evidence source	Some subjects were treated with a second course of teprotumumab in Study HZNP-TEP-302 [OPTIC-X]) and the open-label periods of Studies HZNP-TEP-403 and HZNP-TEP-303 (OPTIC-J). In all 3 studies, teprotumumab was well tolerated in subjects who received a second course.
Population in need of further characterization	The data available are not considered sufficient to fully determine the safety profile after retreatment. Study HZNP-TEP-402, evaluating the safety, tolerability, and need for retreatment of teprotumumab in subjects with TED, is ongoing.

Part II: Module SVIII - Summary of the Safety Concerns

Table 20. Summary of Safety Concerns

Important identified risks	• Hyperglycemia • Exacerbation of inflammatory bowel disease • Infusion-related reactions • Hearing impairment
Important potential risks	• New onset inflammatory bowel disease • Embryofetal toxicity
Missing information	• Safety in retreated patients

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORIZATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

There are no further routine pharmacovigilance activities beyond adverse reaction reporting and signal detection.

III.2 Additional Pharmacovigilance Activities

Table 21. Category 1 to 3 Postauthorization Safety Studies

Study Title and Category Number	Rationale and Study Objectives	Study Design	Study Population	Milestones
Study HZNP-TEP-402 A Phase 3b/4, Double-masked, Randomized, International, Parallel-assignment, Multicenter Trial in Patients with Thyroid Eye Disease to Evaluate the Safety and Tolerability of Different Dosing Durations of Teprotumumab Category 3	Rationale: An FDA postmarketing requirement for a descriptive trial to evaluate the safety, efficacy and need for retreatment of 3 different teprotumumab treatment durations for TED. In addition, serum samples from patients with a Baseline CAS ≥ 3 will be evaluated for biomarkers of disease. Objectives: • To evaluate the safety and tolerability of 3 treatment durations of teprotumumab (4, 8, and 16 infusions) and the need for retreatment. Safety concerns addressed: • Hyperglycemia • Exacerbation of inflammatory bowel disease • Infusion-related reactions • Hearing impairment • New onset inflammatory bowel disease • Safety in retreated patients	Double-masked, randomised, parallel-assignment, multicentre study.	Male or nonpregnant female adult (≥ 18 years) patients with TED.	Final CSR: August 2026
Study HZNP-TEP-402 hearing evaluation substudy Category 3	Rationale: This substudy is an independent, trial to investigate hearing impairment.	Double-masked, randomised, parallel-assignment, multicentre study.	Male or nonpregnant female adult (≥ 18 years) patients with TED.	Final CSR: August 2026

Footnotes, including abbreviations, are defined on the last page of the table.

Table 21. Category 1 to 3 Postauthorization Safety Studies

Study Title and Category Number	Rationale and Study Objectives	Study Design	Study Population	Milestones
Study HZNP-TEP-402 hearing evaluation substudy Category 3 (continued)	Objectives: • To assess the incidence of hearing impairment among TED patients treated with teprotumumab. • To assess the reversibility of hearing impairment at 3 or 6 months post teprotumumab treatment. • To explore potential risk factors associated with ototoxicity among TED patients treated with teprotumumab Safety concerns addressed: • Hearing impairment			
Drug utilization study to evaluate the effectiveness of teprotumumab additional risk minimization measures (aRMMs) (study number TBD) Category 3	Rationale: This planned study will evaluate the effectiveness of teprotumumab aRMMs. Objective: • To quantify indicators of adherence to measures aimed at minimizing the risks of hearing impairment and embryofetal toxicity among patients being prescribed teprotumumab, where fit-for-purpose data are available. Safety concerns addressed: • Hearing impairment • Embryofetal toxicity	Descriptive drug utilization study	Patients with a prescription to teprotumumab as recorded in fit-for-purpose secondary electronic health data sources.	Draft protocol and feasibility report submission: October 2025 Final CSR: April 2033

aRMM = additional risk minimization measure; CSR = clinical study report; FDA = Food and Drug Administration; TBD = to be determined; TED = thyroid eye disease

III.3 Summary Table of Additional Pharmacovigilance Activities

There are no ongoing or planned category 1 or 2 studies. Ongoing and planned category 3 studies are presented below in Table 22.

Table 22. (Table Part III.1) Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required additional pharmacovigilance activities				
Study HZNP-TEP-402 A Phase 3b/4, Double-masked, Randomized, International, Parallel-assignment, Multicenter Trial in Patients with Thyroid Eye Disease to Evaluate the Safety and Tolerability of Different Dosing Durations of Teprotumumab Category 3 Ongoing	• To evaluate the safety and tolerability of 3 treatment durations of teprotumumab (4, 8, and 16 infusions) and the need for retreatment.	• Hyperglycemia • Exacerbation of inflammatory bowel disease • Infusion-related reactions • Hearing impairment • New onset inflammatory bowel disease • Safety in retreated patients	Final CSR	August 2026
Study HZNP-TEP-402 hearing evaluation substudy Category 3 Ongoing	• To assess the incidence of hearing impairment among TED patients treated with teprotumumab. • To assess the reversibility of hearing impairment at 3 or 6 months post teprotumumab treatment. • To explore potential risk factors associated with ototoxicity among TED patients treated with teprotumumab	• Hearing impairment	Final CSR	August 2026

Footnotes, including abbreviations, are defined on the last page of the table.

Table 22. (Table Part III.1) Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required additional pharmacovigilance activities (continued)				
Drug utilization study to evaluate the effectiveness of teprotumumab aRMMs (study number TBD) Planned	• To quantify indicators of adherence to measures aimed at minimizing the risks of hearing impairment and embryofetal toxicity among patients being prescribed teprotumumab, where fit-for-purpose data are available.	• Hearing impairment • Embryofetal toxicity	Draft protocol and feasibility report submission Final CSR	October 2025 April 2033

aRMM = additional risk minimization measure; CSR = clinical study report; TBD = to be determined; TED = thyroid eye disease

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

Not applicable.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

Risk Minimization Plan

V.1 Routine Risk Minimization Measures

Table 23. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Identified Risks	
Hyperglycemia	Routine risk communication: • SmPC Sections 4.4 and 4.8 • PL Sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation to assess patients for elevated blood glucose and symptoms of hyperglycemia prior to infusion as well as during treatment, ensure that patients with hyperglycemia or pre-existing diabetes are under appropriate glycemic control before and while receiving teprotumumab, and to monitor blood glucose for 6 months after completion of treatment with teprotumumab is provided in SmPC Section 4.4. Other risk minimization measures beyond the PI: • Legal Status: prescription only medicine
Exacerbation of inflammatory bowel disease	Routine risk communication: • SmPC Sections 4.4 and 4.8 • PL Sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation to monitor patients with IBD for flare of disease and to consider discontinuation of treatment if IBD exacerbation is suspected is provided in SmPC Section 4.4. Other risk minimization measures beyond the PI: • Legal Status: prescription only medicine

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 23. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Identified Risks (continued)	
Infusion-related reactions	Routine risk communication: • SmPC Sections 4.2, 4.4, and 4.8 • PL Sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation to premedicate and/or administer all subsequent infusions at a slower rate in patients experiencing immediate hypersensitivity is provided in SmPC Sections 4.2 and 4.4. • Instruction to monitor patients throughout infusion and for 90 minutes after treatment; to interrupt or discontinue the infusion based on severity of the infusion-related reaction and to manage the reaction appropriately is included in SmPC Section 4.4. • Guidance on signs and symptoms of infusion-related reactions and the importance of reporting to the physician or seeking medical help immediately is provided in PL Section 2. • Guidance on the importance of reporting infusion-related reactions to the physician or nurse straight away is provided in PL Section 4. Other risk minimization measures beyond the PI: • Legal Status: prescription only medicine

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 23. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Identified Risks (continued)	
Hearing impairment	Routine risk communication: • SmPC Sections 4.4 and 4.8 • PL Sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendations are provided in SmPC Section 4.4: - to advise patients to report symptoms of altered hearing promptly to their healthcare professional - to consider the benefit-risk of treatment in patients with pre-existing hearing impairment - to assess patients' hearing using audiometry before starting treatment (first infusion), during treatment (around the third or fourth infusion), and after completing treatment with teprotumumab - to perform additional audiometric assessments as necessary if a patient experiences subjective hearing changes during treatment, and to monitor hearing in these patients for up to 6 months after completion of treatment - to discontinue teprotumumab in patients experiencing hearing loss that requires intervention, limits their ability to self-care, or is considered profound - to advise patients to stop smoking and avoid high intensity noises during treatment, and that blood pressure should be appropriately controlled before and while receiving teprotumumab - to use caution when co-administering teprotumumab in patients who are receiving concomitant therapies known to cause ototoxicity • Guidance on the importance of reporting any changes in hearing to the physician as soon as possible is provided in PL Sections 2 and 4. Other routine risk minimization measures beyond the Product Information: • Legal Status: prescription only medicine

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 23. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Potential Risks	
New onset inflammatory bowel disease	Routine risk communication: • None Routine risk minimization activities recommending specific clinical measures to address the risk: • None Other routine risk minimization measures beyond the PI: • Legal Status: prescription only medicine
Embryofetal toxicity	Routine risk communication: • SmPC Sections 4.3, 4.4, 4.6, and 5.3. • PL Section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: • Use of teprotumumab in pregnancy is contraindicated in SmPC Section 4.3. • Recommendation that women of childbearing potential should use effective contraception during and for at least 6 months after the last administration of teprotumumab is provided in SmPC Section 4.4. • Recommendation that women of childbearing potential should use effective contraception (methods that result in less than 1% pregnancy rates) prior to initiation, during treatment, and for at least 6 months after the last administration of teprotumumab is provided in SmPC Section 4.6. Other routine risk minimization measures beyond the PI: • Legal Status: prescription only medicine
Missing Information	
Safety in retreated patients	Routine risk communication: • SmPC Section 4.2 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation that additional doses should not be administered if response is not achieved with the treatment regimen for teprotumumab is provided in SmPC Section 4.2. Other routine risk minimization measures beyond the PI: • Legal Status: prescription only medicine

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IBD = inflammatory bowel disease; IV = intravenous; PI = product information; PL = package leaflet; SmPC = Summary of Product Characteristics

V.2 Additional Risk Minimization Measures

Table 24. Additional Risk Minimization Measure: Healthcare Professional Guide

Objectives	A Healthcare Professional Guide is provided to address the following risks: • Hearing impairment • Embryofetal toxicity
Rationale for the additional risk minimization activity	Rationale: • Reinforcement of signs and symptoms of hearing impairment may facilitate early diagnosis and treatment. • To ensure risk of exposure of an unborn child to teprotumumab is minimized.
Target audience and planned distribution path	Target audience is healthcare professionals involved in patient care. Distribution is by hard copy, email, or any other means as deemed appropriate, on a country by country basis in accordance with competent authority requirements.
Plans to evaluate the effectiveness of the interventions and criteria for success	Amgen is planning to perform a drug utilization study to evaluate the effectiveness of aRMMs for teprotumumab using secondary healthcare data, with the objective of quantifying indicators of adherence to measures aimed at minimizing the risks of hearing impairment and embryofetal toxicity among patients being prescribed teprotumumab.
Evaluation of the effectiveness of risk minimization activities	Not yet assessed.

aRMM = additional risk minimization measure; EU = European Union

Table 25. Additional Risk Minimization Measure: Patient Guide

Objectives	A Patient Guide is provided to address the following risks: • Hearing impairment • Embryofetal toxicity
Rationale for the additional risk minimization activity	Rationale: • To advise that teprotumumab may cause hearing impairment. • To advise that teprotumumab may cause harm to an unborn child.
Target audience and planned distribution path	Patients who are treated with teprotumumab will receive the Patient Guide from the healthcare professional. Distribution is by hard copy, email, or any other means as deemed appropriate, on a country by country basis in accordance with competent authority requirements.
Plans to evaluate the effectiveness of the interventions and criteria for success	Amgen is planning to perform a drug utilization study to evaluate the effectiveness of aRMMs for teprotumumab, with the objective of quantifying indicators of adherence to measures aimed at minimizing the risks of hearing impairment and embryofetal toxicity among patients being prescribed teprotumumab.
Evaluation of the effectiveness of risk minimization activities	Not yet assessed.

aRMM = additional risk minimization measure

V.3 Summary of Risk Minimization Measures

Table 26. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks		
Hyperglycemia	Routine risk minimization measures: • SmPC Section 4.4, where a recommendation to assess patients for elevated blood glucose and symptoms of hyperglycemia prior to infusion as well as during treatment, ensure that patients with hyperglycemia or pre-existing diabetes are under appropriate glycemic control before and while receiving teprotumumab, and to monitor blood glucose for 6 months after completion of treatment with teprotumumab is provided. • SmPC Section 4.8 • PL Sections 2 and 4 • Legal Status: prescription only medicine Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study HZNP-TEP-402
Exacerbation of inflammatory bowel disease	Routine risk minimization measures: • SmPC Section 4.4, where a recommendation to monitor patients with IBD for flare of disease and to consider discontinuation treatment if IBD exacerbation is suspected is provided. • SmPC Section 4.8 • PL Sections 2 and 4 • Legal Status: prescription only medicine Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study HZNP-TEP-402

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 26. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks (continued)		
Infusion-related reactions	Routine risk minimization measures: • SmPC Sections 4.2 and 4.4, where a recommendation to premedicate and/or administer all subsequent infusions at a slower rate in patients experiencing immediate hypersensitivity is provided. • SmPC Section 4.4, where instructions to monitor patients throughout infusion and for 90 minutes after treatment, to interrupt or discontinue the infusion based on severity of the infusion-related reaction, and to manage the reaction appropriately is included. • SmPC Section 4.8 • PL Section 2, where guidance on signs and symptoms of infusion-related reactions and the importance of reporting to the physician or seeking medical help immediately is provided. • PL Section 4, where guidance on the importance of reporting infusion-related reactions to the physician or nurse straight away is provided. • Legal Status: prescription only medicine Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study HZNP-TEP-402

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 26. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks (continued)		
Hearing impairment	Routine risk minimization measures: • SmPC Section 4.4, where recommendations are provided: - to advise patients to report symptoms of altered hearing promptly to their healthcare professional - to consider the benefit-risk of treatment in patients with pre-existing hearing impairment - to assess patients' hearing using audiometry before starting treatment (first infusion), during treatment (around the third or fourth infusion), and after completing treatment with teprotumumab - to perform additional audiometric assessments as necessary if a patient experiences subjective hearing changes during treatment, and to monitor hearing in these patients for up to 6 months after completion of treatment - to discontinue teprotumumab in patients experiencing hearing loss that requires intervention, limits their ability to self-care, or is considered profound - to advise patients to stop smoking and avoid high intensity noises during treatment, and that blood pressure should be appropriately controlled before and while receiving teprotumumab - to use caution when co-administering teprotumumab in patients who are receiving concomitant therapies known to cause ototoxicity • SmPC Section 4.8 • PL Sections 2 and 4 where guidance on the importance of reporting any changes in hearing to the physician as soon as possible is provided. • Legal Status: prescription only medicine Additional risk minimization measures: • Healthcare Professional Guide • Patient Guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study HZNP-TEP-402 • Substudy HZNP-TEP-402 • Drug utilization study (study number TBD)

Footnotes, including abbreviations, are defined on the last page of the table.

Table 26. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Potential Risks		
New onset inflammatory bowel disease	Routine risk minimization measures: • Legal Status: prescription only medicine Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study HZNP-TEP-402
Embryofetal toxicity	Routine risk minimization measures: • SmPC Section 4.3 where use of teprotumumab in pregnancy is contraindicated. • SmPC Section 4.4 where a recommendation that women of childbearing potential should use effective contraception during and for at least 6 months after the last administration of teprotumumab is included. • SmPC Section 4.6 where a recommendation that women of childbearing potential should use effective contraception (methods that result in less than 1% pregnancy rates) prior to initiation, during treatment, and for at least 6 months after the last administration of teprotumumab is included. • SmPC Section 5.3 • PL Section 2 • Legal Status: prescription only medicine Additional risk minimization measures: • Healthcare Professional Guide • Patient Guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Drug utilization study (study number TBD)

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 26. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Missing information		
Safety in retreated patients	Routine risk minimization measures: • SmPC Section 4.2 where a recommendation that additional doses should not be administered if response is not achieved with the treatment regimen for teprotumumab is included. • Legal Status: prescription only medicine Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study HZNP-TEP-402

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IBD = inflammatory bowel disease; PL = package leaflet; SmPC = Summary of Product Characteristics; TBD = to be determined

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

A summary of the risk management plan (RMP) for teprotumumab is presented below.

Summary of Risk Management Plan for Tepezza® (teprotumumab)

This is a summary of the RMP for Tepezza. The RMP details important risks of Tepezza, how these risks can be minimized, and how more information will be obtained about Tepezza's risks and uncertainties (missing information).

Tepezza's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Tepezza should be used.

This summary of the RMP for Tepezza should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Tepezza's RMP.

I. The Medicine and What it is Used for

Tepezza is authorized for the treatment of moderate to severe Thyroid Eye Disease (TED) (see SmPC for the full indication). It contains teprotumumab as the active substance and it is given by intravenous administration.

Further information about the evaluation of Tepezza's benefits can be found in Tepezza's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/tepezza

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Tepezza, together with measures to minimize such risks and the proposed studies for learning more about Tepezza's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status - the way a medicine is supplied to the public (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In the case of Tepezza, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Tepezza is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of Tepezza are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Tepezza. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Hyperglycemia • Exacerbation of inflammatory bowel disease • Infusion-related reactions • Hearing impairment
Important potential risks	• New onset inflammatory bowel disease • Embryofetal toxicity
Missing information	• Safety in retreated patients

II.B. Summary of Important Risks

Important identified risk: Hyperglycemia	
Evidence for linking the risk to the medicine	The risk was identified in randomized controlled clinical trials and further confirmed from postmarketing data.
Risk factors and risk groups	Risk groups: • Patients with pre-existing diabetes mellitus. • Patients with impaired glucose tolerance
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4, where a recommendation to assess patients for elevated blood glucose and symptoms of hyperglycemia prior to infusion as well as during treatment, ensure that patients with hyperglycemia or pre-existing diabetes are under appropriate glycemic control before and while receiving teprotumumab, and to monitor blood glucose for 6 months after completion of treatment with teprotumumab is provided. • SmPC Section 4.8 • PL Sections 2 and 4 • Legal Status: prescription only medicine Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study HZNP-TEP-402 See Section II.C of this summary for an overview of the postauthorization development plan.

Important identified risk: Exacerbation of inflammatory bowel disease	
Evidence for linking the risk to the medicine	The risk was identified in randomized controlled clinical trials.
Risk factors and risk groups	Risk groups: • Patients with known history of IBD (ulcerative colitis or Crohn's disease). • Patients with family history of IBD (Ashraf et al, 2021)
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4, where a recommendation to monitor patients with IBD for flare of disease and to consider discontinuation of treatment if IBD exacerbation is suspected is provided. • SmPC Section 4.8 • PL Sections 2 and 4 • Legal Status: prescription only medicine Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study HZNP-TEP-402 See Section II.C of this summary for an overview of the postauthorization development plan.

Important identified risk: Infusion-related reactions	
Evidence for linking the risk to the medicine	The risk was identified in randomized controlled clinical trials and further confirmed from postmarketing data.
Risk factors and risk groups	Risk group: • Patients with known history of hypersensitivity and infusion-related reactions
Risk minimization measures	Routine risk minimization measures: • SmPC Sections 4.2 and 4.4, where a recommendation to premedicate and/or administer all subsequent infusions at a slower rate in patients experiencing immediate hypersensitivity is provided. • SmPC Section 4.4, where instructions to monitor patients throughout infusion and for 90 minutes after treatment; to interrupt or discontinue the infusion based on severity of the infusion-related reaction and to manage the reaction appropriately is included. • SmPC Section 4.8 • PL Section 2, where guidance on signs and symptoms of infusion-related reactions and the importance of reporting to the physician or seeking medical help immediately is provided. • PL Section 4, where guidance on the importance of reporting infusion-related reactions to the physician or nurse straight away is provided. • Legal Status: prescription only medicine Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study HZNP-TEP-402 See Section II.C of this summary for an overview of the postauthorization development plan.

Important identified risk: Hearing impairment	
Evidence for linking the risk to the medicine	Overall, during the development program, hearing impairment occurred at a higher incidence among participants in the teprotumumab group compared to the placebo group. In the postmarketing setting, cases of hearing impairment have been reported, some of which have been severe.
Risk factors and risk groups	There are no data on risk factors or risk groups for patients with TED treated with teprotumumab.

Important identified risk: Hearing impairment (continued)	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4, where recommendations are provided: - to advise patients to report symptoms of altered hearing promptly to their healthcare professional - to consider the benefit-risk of treatment in patients with pre-existing hearing impairment - to assess patients' hearing using audiometry before starting treatment (first infusion), during treatment (around the third or fourth infusion), and after completing treatment with teprotumumab - to perform additional audiometric assessments as necessary if a patient experiences subjective hearing changes during treatment, and to monitor hearing in these patients for up to 6 months after completion of treatment - to discontinue teprotumumab in patients experiencing hearing loss that requires intervention, limits their ability to self-care, or is considered profound - to advise patients to stop smoking and avoid high intensity noises during treatment, and that blood pressure should be appropriately controlled before and while receiving teprotumumab - to use caution when co-administering teprotumumab in patients who are receiving concomitant therapies known to cause ototoxicity • SmPC Section 4.8 • PL Sections 2 and 4 where guidance on the importance of reporting any changes in hearing to the physician immediately is provided. • Legal Status: prescription only medicine Additional risk minimization measures: • Healthcare Professional Guide • Patient Guide
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study HZNP-TEP-402 • Substudy HZNP-TEP-402 • Drug utilization study (study number to be determined) See Section II.C of this summary for an overview of the postauthorization development plan.

Important potential risk: New onset inflammatory bowel disease	
Evidence for linking the risk to the medicine	It is difficult to distinguish new onset IBD and exacerbation of pre-existing IBD based on clinical manifestations. In addition, the possible biological plausibility that teprotumumab may cause IBD worsening (see above) is also applicable to new onset IBD. At this time, there are no safety reports of new onset IBD in trials. There were 2 solicited cases reporting new onset IBD for which medical history, physician confirmation, or time to onset is not available. As such, new onset IBD is considered an important potential risk.
Risk factors and risk groups	Risk groups: • Patients with family history of IBD (Ashraf et al, 2021)
Risk minimization measures	Routine risk minimization measures: • Legal Status: prescription only medicine Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study HZNP-TEP-402 See Section II.C of this summary for an overview of the postauthorization development plan.

Important potential risk: Embryofetal toxicity	
Evidence for linking the risk to the medicine	The source of information is nonclinical study (animal) data and its mechanism of action as insulin-like growth factor-1 receptor inhibitor.
Risk factors and risk groups	There are no known risk factors for embryofetal toxicity in patients treated with teprotumumab. Risk groups: • Women planning to become pregnant; • Women of childbearing potential not using effective birth control measures; • Pregnant women (Douglas et al, 2021).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.3 where use of teprotumumab in pregnancy is contraindicated. • SmPC Section 4.4 where a recommendation that women of childbearing potential should use effective contraception during and for at least 6 months after the last administration of teprotumumab is included. • SmPC Section 4.6 where a recommendation that women of childbearing potential should use effective contraception (methods that result in less than 1% pregnancy rates) prior to initiation, during treatment, and for at least 6 months after the last administration of teprotumumab is included. • SmPC Section 5.3 • PL Section 2 • Legal Status: prescription only medicine Additional risk minimization measures: • Healthcare Professional Guide • Patient Guide
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Drug utilization study (study number to be determined) See Section II.C of this summary for an overview of the postauthorization development plan.

Missing information: Safety in retreated patients	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2 where a recommendation that additional doses should not be administered if response is not achieved with the treatment regimen for teprotumumab is included. • Legal Status: prescription only medicine Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study HZNP-TEP-402 See Section II.C of this summary for an overview of the postauthorization development plan.

II.C. Postauthorization Development Plan

II.C.1. Studies Which Are Conditions of the Marketing Authorization

At this time, there are no studies which are conditions of the marketing authorization or specific obligation of Tepezza.

II.C.2. Other Studies in Postauthorization Development Plan

Study Short Name	Purpose of the Study
Study HZNP-TEP-402 A Phase 3b/4, Double-masked, Randomized, International, Parallel assignment, Multicenter Trial in Patients with Thyroid Eye Disease to Evaluate the Safety and Tolerability of Different Dosing Durations of Teprotumumab Category 3	The primary objective is to evaluate the safety and tolerability of 3 treatment durations of Tepezza (4, 8 and 16 infusions) and the need for retreatment.
Study HZNP-TEP-402 hearing evaluation substudy Category 3	The objectives include: • To assess the incidence of hearing impairment among TED patients treated with teprotumumab. • To assess the reversibility of hearing impairment at 3 or 6 months post teprotumumab treatment. • To explore potential risk factors associated with ototoxicity among TED patients treated with teprotumumab
Drug utilization study to evaluate the effectiveness of teprotumumab aRMMs (study number to be determined) Category 3	Objective: • To quantify indicators of adherence to measures aimed at minimizing the risks of hearing impairment and embryofetal toxicity among patients being prescribed teprotumumab, where fit-for-purpose data are available.

PART VII: ANNEXES

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Annex 4. Specific Adverse Drug Reaction Follow-up Forms

Not applicable.

Annex 6. Details of Proposed Additional Risk Minimization Activities (if Applicable)

Draft key messages of the additional risk minimization measures

Prior to the use of Tepezza in each Member State, the Marketing Authorization 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 embryofetal toxicity.
- Provision of information to patients for the risks of hearing impairment and embryofetal 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 embryofetal 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 fetus.
    - 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.