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Swiss Summary of the Risk Management Plan (RMP) for TEPEZZA® (TEPROTUMUMAB)
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The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them.

The RMP summary of TEPEZZA® is a concise document and does not claim to be exhaustive.
As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.
Please note that the reference document which is valid and relevant for the effective and safe use of TEPEZZA® in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic.

AMGEN Switzerland AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of TEPEZZA®.

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.

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 (e.g., 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 Missing information	• New onset inflammatory bowel disease • Embryofetal toxicity • Safety in retreated patients

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 Postauthorization Development Plan of this summary for an overview

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 Postauthorization Development Plan of this summary for an overview

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 Postauthorization Development Plan of this summary for an overview

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
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 Postauthorization Development Plan of this summary for an overview

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 Postauthorization Development Plan of this summary for an overview

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 Postauthorization Development Plan of this summary for an overview

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 Postauthorization Development Plan of this summary for an overview

Postauthorization Development Plan

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.

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.	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. 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
Study HZNP-TEP-402 hearing evaluation substudy Category 3	
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.

Summary of changes to the risk management plan over time

Not applicable.