Emgality®

galcanezumab

solution for injection 120 mg/ml

Summary of Risk Management Plan (RMP)

Summary of the risk management plan (RMP) for Emgality (galcanezumab)
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 Emgality 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 Emgality in Switzerland is the „Arzneimittelinformation/ Information sur le médicament“ (see www.swissmedicinfo.ch) approved and authorized by Swissmedic.
Eli Lilly is fully responsible for the accuracy and correctness of the content of this published summary RMP of Emgality.

I. The Medicine and What It Is Used for

Emgality is authorised for prophylaxis of migraine in adults who have at least 4 migraine days per month (see SmPC for the full indication). It contains galcanezumab as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of Emgality's benefits can be found in Emgality's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Measures to minimise the risks identified for Emgality include:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;

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

Measures to minimise the risks identified for medicinal products include:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.

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

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including Periodic Safety Update Report 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 Emgality is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of Emgality are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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 Emgality. 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	Serious hypersensitivity
Important potential risks	Serious cardiovascular outcomes in patients at high risk of cardiovascular and cerebrovascular events Hypertension during pregnancy and pre-eclampsia
Missing information	Use in pregnancy Long-term safety including malignancies

II.B. Summary of Important Risks

Important Identified Risk: Serious Hypersensitivity	
Evidence for linking the risk to the medicine	Antidrug antibody levels that developed after starting galcanezumab did not appear to impact its safety profile in patients who had reported hypersensitivity events. This applied regardless of duration of galcanezumab exposure and magnitude of the antidrug antibody levels measured. The current evidence is from the clinical development programme and from postmarketing reports. In the clinical development programme, hypersensitivity events were observed at a higher incidence in galcanezumab-treated patients compared to placebo. This finding was consistently observed across all the clinical trials with galcanezumab, and the evidence was considered sufficient to conclude that some hypersensitivity reactions (urticaria, pruritus, and injection site reactions) were adverse effects of the product. The profile in the clinical development programme has been mainly characterised by skin events (urticaria and pruritus), which were mild or moderate in severity and associated with nonserious outcomes. Relatively low patient exposure in the trials did not allow detection of rare hypersensitivity events. However, post-marketing cases of serious hypersensitivity reactions, including anaphylaxis, angioedema, and urticaria, have been reported.
Risk factors and risk groups	Patients with a history of hypersensitivity to monoclonal antibodies or therapeutic proteins were excluded from the clinical development programme, therefore it is not known if previous hypersensitivity to another biological product constitutes a risk factor for treatment with galcanezumab. No significant dose-response has been observed between the galcanezumab 120 mg and the 240 mg dose groups in the frequency of hypersensitivity TEAEs. No trend for an increase in the by-monthly frequency of hypersensitivity events is evident with additional exposure to galcanezumab.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.8 and PL Section 2 SmPC Section 4.3 includes a contraindication in patients with known hypersensitivity to galcanezumab or to any of the excipients. SmPC Section 4.4 provides guidance to discontinue galcanezumab and start appropriate therapy if a serious hypersensitivity reaction occurs. PL Section 4 provides guidance to the patient to stop using galcanezumab and tell their doctor if they think that they have had an allergic reaction.

Additional pharmacovigilance activities	Additional pharmacovigilance activities: Galcanezumab European Drug Utilisation and Safety Outcomes Study Galcanezumab US Drug Utilisation and Safety Outcomes Study See Section II.C of this summary for an overview of the post-authorisation development plan.

Abbreviations: PL = package leaflet; SmPC = summary of product characteristics; TEAEs = treatment-emergent adverse events.

Important Potential Risk: Serious Cardiovascular Outcomes in Patients at High Risk of Cardiovascular and Cerebrovascular Events	
Evidence for linking the risk to the medicine	Data from the clinical development programme reported in this Marketing Authorisation Application have not demonstrated a signal for serious cardiovascular events for up to 1 year of exposure to galcanezumab. There is therefore no current evidence that serious cardiovascular risk either is an adverse effect of galcanezumab nor has any ostensible impact on the benefit-risk profile. However, relatively few patients have been exposed for up to 1 year and long-term data in a chronic condition such as migraine are missing, so the implications of chronic CGRP inhibition in patients remain uncertain. This uncertainty notably relates to cardiovascular safety given that nonclinical studies suggest that CGRP plays an important role in facilitating vasodilatation to various stimuli including acute ischaemia and the target population is at higher risk of ischaemic cardiovascular outcomes. Patients with a medical history or pre-existing CVD, or risk factors for cardiovascular events were included in the Phase 3 clinical trials, with approximately 17% to 19% of patients identified with pre-existing cardiac risk factors. However, patients with recent acute cardiovascular events and/or serious cardiovascular risk within the 6 months before enrolment were excluded from the Phase 3 migraine trials. In addition, patients with a lifetime history of stroke were excluded from 2 Phase 3 studies. As a result, the cardiovascular safety of the product in the migraine population at higher risk represents a gap in knowledge.
Risk factors and risk groups	No specific risk factors have been identified for cardiovascular outcomes in patients treated with galcanezumab.
Risk minimisation measures	Routine risk minimisation measures • SmPC Section 4.4 states that patients with certain major cardiovascular diseases were excluded from clinical studies and cross-references to section 5.1 for additional details on these patients. • PL Section 2 advises patients to inform their HCP if they have serious cardiovascular disease.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Galcanezumab European Drug Utilisation and Safety Outcomes Study Galcanezumab US Drug Utilisation and Safety Outcomes Study See Section II.C of this summary for an overview of the post-authorisation development plan.

Important Potential Risk: Hypertension During Pregnancy and Pre-eclampsia	
Evidence for linking the risk to the medicine	The majority of patients with migraine are females of child-bearing age; therefore, pregnancy is likely to occur in women who are exposed to galcanezumab. In addition, women with migraine are thought to be at an increased risk for pre-eclampsia compared to women without migraine, due to disordered reactivity of the blood vessels and abnormal platelet activity. Studies performed in multiple countries have demonstrated that women with migraine experience a 1.4 - 4.0 fold increased risk of pre-eclampsia relative to non-migraine controls. There was no evidence of an increased risk of hypertension or pre-eclampsia in patients exposed to galcanezumab in pregnancy during clinical development; however, experience in pregnancy was very limited. Of 16 pregnancies, reported, one mother experienced pre-eclampsia (6.25% of pregnancies). This is consistent with the World Health Organisation's global estimate of pre-eclampsia in the general population (2-8%). Given the biological mechanism of galcanezumab and the role of CGRP in pregnancy, there is a theoretical rationale for including hypertension and pre-eclampsia, as an important potential risk among women with migraine who are exposed to galcanezumab during pregnancy.
Risk factors and risk groups	Other than the subset of treated migraine patients who become pregnant who, in general are at higher risk of hypertension in pregnancy or pre-eclampsia, no specific risk factors have been identified for galcanezumab as experience of pre-eclampsia is confined to one case (6.25%). <u>Preventability:</u> Current experience of the use of galcanezumab in pregnancy and hypertension /pre-eclampsia is too limited to provide data on the predictability of the potential risk or factors that could increase the risk. Routine management of pregnancy, irrespective of any treatment received, includes regular blood pressure monitoring as a standard measure. In these circumstances, it would be expected that clinically concerning increases in BP as a possible predictor of pre-eclampsia would be detected as part of standard clinical practice.
Risk minimisation measures	Routine risk minimisation measures • None beyond proposed wording for use in pregnancy in SmPC Section 4.6 and section 2 of the PL.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Cohort Study of Exposure to Galcanezumab during Pregnancy See Section II.C of this summary for an overview of the post-authorisation development plan.

Abbreviations: BP = blood pressure; CGRP = calcitonin gene-related peptide; CVD = cardiovascular disease; EU = European Union; GVP = good pharmacovigilance practice; HCP = health care professional; SmPC = summary of product characteristics.

Missing Information: Use in Pregnancy	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.6 provides guidance that as a precautionary measure, it is preferable to avoid the use of galcanezumab during pregnancy. Emgality could be considered during breastfeeding only if clinically needed. It is specifically recommended that women of childbearing potential use an effective method of contraception during treatment and for at least 5 months after treatment. • PL Section 2 advises women to avoid becoming pregnant while using galcanezumab and also recommends using contraception while using Emgality and for at least 5 months after the last Emgality dose. Women who are breast-feeding or planning to breast-feed are advised to talk to their doctor before using this medicine.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Cohort Study of Exposure to Galcanezumab during Pregnancy See Section II.C of this summary for an overview of the post-authorisation development plan.

Abbreviations: SmPC = summary of product characteristics.

Missing Information: Long-Term Safety Including Malignancies	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 5.3
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Galcanezumab European Drug Utilisation and Safety Outcomes Study Galcanezumab US Drug Utilisation and Safety Outcomes Study See Section II.C of this summary for an overview of the post-authorisation development plan.

Abbreviations: SmPC = summary of product characteristics.

II.C. Post-Authorisation Development Plan

II.C.1. Studies That Are Conditions of the Marketing Authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of Emgality.

II.C.2. Other Studies in Post-Authorisation Development Plan

Study short name: Cohort Study of Exposure to Galcanezumab during Pregnancy

Purpose of the study:
Pregnant women were not included in the clinical development programme; however, the indicated population is predominantly women, many whom are of childbearing age. The population of pregnant women treated with galcanezumab is therefore one which warrants further characterisation, as effects on the foetus after exposure in utero are unknown. For risk management purposes, this represents missing information as adverse outcomes in pregnancy could impact benefit-risk. Additionally, some non-clinical studies have shown that CGRP is an important factor in blood pressure regulation during pregnancy and that low CGRP levels have been associated with pre-eclampsia. Given that there is a theoretical rationale for hypertension during pregnancy and pre-eclampsia, these are considered to be important potential risks. This post-authorisation observational study will actively monitor exposure to galcanezumab during pregnancy among women with migraine or cluster headache, study the incidence of pregnancy outcomes (including hypertension during pregnancy and pre-eclampsia) in women with galcanezumab exposure, and compare the incidence of pregnancy outcomes to other women with migraine, including those receiving other prophylactic medication for the treatment of migraine.

Study short name: Galcanezumab European Drug Utilisation and Safety Outcomes Study

Purpose of the study:

The longer-term safety of galcanezumab (beyond 1 year) has not been established through the clinical trial programme. Migraine is a chronic condition; therefore, long-term galcanezumab use beyond 1 year is reasonably anticipated in routine clinical practice. Therefore, adverse effects which are infrequent, have a longer latency period such as malignancy, and/or are infrequent among migraine patients such as serious hypersensitivity could occur. Additionally, patients with recent acute cardiovascular events and/or serious cardiovascular risk, as well as patients over the age of 65, were excluded from the clinical trial population and use in this group of patients may also occur in everyday clinical practice. The implications of long-term inhibition of CGRP are unknown, including the impact on long-term safety. As a result, the long-term safety of galcanezumab in larger patient populations requires further characterisation

The objective of this study is to evaluate the utilisation and long-term safety of galcanezumab, including cardiovascular safety, malignancy, and serious hypersensitivity events in routine clinical practice.

The secondary objective is to provide context for incidence rates of safety events seen in the galcanezumab cohort by describing the incidence rates observed in a comparator cohort and, as feasible, to conduct comparative safety analyses of serious cardiovascular events, serious

hypersensitivity reactions, and malignancies using patients initiated on other prophylactic migraine medication as a control.

Study short name: Galcanezumab US Drug Utilisation and Safety Outcomes Study

Purpose of the study:

The longer-term safety of galcanezumab (beyond 1 year) has not been established through the clinical trial programme. As migraine is a chronic condition, potential longer-term use beyond 1 year is anticipated in routine clinical practice. Therefore, adverse effects that have a longer latency period such as malignancy, and/or are infrequent among migraine patients such as serious hypersensitivity could occur. Additionally, patients with recent acute cardiovascular events and/or serious cardiovascular risk, as well as patients over the age of 65, were excluded from the clinical trial population and use in this group of patients may also occur in everyday clinical practice. The implications of long-term inhibition of CGRP are unknown, including the impact on long-term safety. As a result, the long-term safety of galcanezumab in larger patient populations requires further characterisation.

The objective of this study is to evaluate the utilisation and long-term safety of galcanezumab, including cardiovascular safety, malignancy, and serious hypersensitivity events in routine clinical practice.

The study also aims to understand the risk of specified safety events in patients receiving galcanezumab relative to adult patients who initiated treatment with another prophylactic migraine medication. Safety events observed in the primary objective will inform the design of comparative analyses.

Major Changes to the Risk Management Plan over Time

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This summary was last updated in 01-2024