

Part VI: Summary of the risk management plan

Summary of risk management plan for VYEPTI[®] (eptinezumab)

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

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

This summary of the RMP for VYEPTI should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all 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 VYEPTI's RMP.

I. The medicine and what it is used for

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

Further information about the evaluation of VYEPTI's benefits will be available in VYEPTI's EPAR, including in its plain-language summary, available under the medicine's webpage:

<https://www.ema.europa.eu/en/medicines/human/EPAR/vyepti>

II. Risks associated with the medicine and activities to minimise or further characterise the risks

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

Measures to minimise 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 authorised 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 patient (e.g. with or without prescription) can help to minimise its risks.

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

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed 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 VYEPTI is not yet available, it is listed under ‘missing information’ below.

II.A List of important risks and missing information

Important risks of VYEPTI are risks that need special risk management activities to further investigate or minimise 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 VYEPTI. 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	None
Important potential risks	Cardiovascular outcomes in patients with pre-existing myocardial infarction, cerebrovascular accident, transient ischemic attack, angina unstable and poorly controlled hypertension Pre-eclampsia
Missing information	Use in pregnant women Long-term safety

II.B Summary of important risks

Important potential risk: Cardiovascular outcomes in patients with pre-existing myocardial infarction, cerebrovascular accident, transient ischemic attack, angina unstable and poorly controlled hypertension	
Evidence for linking the risk to the medicine	The important potential risk is based upon the mechanism of action of CGRP inhibition and the theoretical concern for cardiovascular risk. There is presently no evidence to suggest that eptinezumab has a negative impact on patients with pre-existing cardiovascular conditions. Data from the eptinezumab clinical studies showed no indication for an increased cardiovascular risk. Cardiovascular Treatment-Emergent Adverse Events were reported at low incidences with no difference between eptinezumab and placebo treatment groups. No significant changes in hemodynamic and ECG parameters were seen. However, as patients with pre-existing cardiovascular conditions were excluded from the clinical

	development program, limited data is available in use in this population.
Risk factors and risk groups	As this potential risk is based upon a theoretical concern related to the mechanism of action of CGRP inhibition and no actual increased cardiovascular risk has been established, risk factors or risk groups, if any, are unknown.
Risk minimisation measures	Routine risk minimisation measures Section 4.4 (Special Warnings and Precaution for use) of the SmPC includes information that patients with a history of cardiovascular disease were excluded from the clinical trials and no safety data are available for these patients. Section 4.4 of the SmPC also includes information that limited data is available in patients with cardiovascular risk factors. No additional risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Long-Term Cardiovascular Safety and Real-World Use of Eptinezumab Study

Important potential risk: Pre-eclampsia	
Evidence for linking the risk to the medicine	The important potential risk is based upon the mechanism of action of CGRP inhibition and the theoretical concern for a potential association with hypertension and hence pre-eclampsia. However, there is currently no evidence to suggest that eptinezumab may have a negative impact on human pregnancy. The clinical studies with eptinezumab showed no increased risk in hypertension or increased blood pressure and no events of pre-eclampsia have been reported. However, limited data is available in use during pregnancy.
Risk factors and risk groups	As this potential risk is based upon a theoretical concern related to the mechanism of action of CGRP inhibition and no actual increased risk for pre-eclampsia has been established, risk factors or risk groups, if any, are unknown.
Risk minimisation measures	Routine risk minimisation measures Section 4.6 (Fertility, Pregnancy and Lactation) of the SmPC states that limited data is available on use in pregnancy and includes advice that it is preferable to avoid the use of eptinezumab during pregnancy. No additional risk minimisation measures

Additional pharmacovigilance activities	Additional pharmacovigilance activities: Eptinezumab Post-marketing Pregnancy Program
---	--

Missing information: Use in pregnant women	
Risk minimisation measures	Routine risk minimisation measures Section 4.6 (Fertility, Pregnancy and Lactation) of the SmPC states that limited data is available on use in pregnancy and includes advice that it is preferable to avoid the use of eptinezumab during pregnancy No additional risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Eptinezumab Post-marketing Pregnancy Program

Missing information: Long-term safety	
Risk minimisation measures	No routine risk minimisation measures No additional risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Long-term Cardiovascular Safety and Real-World Use of Eptinezumab Study

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of VYEPTI.

II.C.2 Other studies in post-authorisation development plan

Long-term Cardiovascular Safety and Real-World use of Eptinezumab Study

Purpose of the study:

Migraine is a chronic condition. Therefore, long-term eptinezumab use is expected in routine clinical practice. Adverse events such as cardiovascular diseases might be infrequent and might appear only after long-term patient exposure. However, data on exposures beyond 1 year is limited and the safety of eptinezumab beyond 2 years has not been investigated in the clinical trial program. Additionally, patients with recent acute cardiovascular events and/or serious cardiovascular risk were excluded from the clinical trial population and use in this group of patients may also occur in everyday clinical practice. Therefore, long-term cardiovascular safety, including the safe use of eptinezumab in patients with a known history of cardiovascular disease, requires further characterization in real life routine clinical practice.

The objective of this study is to assess the long-term cardiovascular risk in patients treated with eptinezumab, including the evaluation of the impact on a known history of cardiovascular diseases on the long-term cardiovascular risk. Furthermore, the study will also characterize the utilization of eptinezumab in routine clinical practice.

Eptinezumab Post-marketing Pregnancy Program

Purpose of the study:

Migraine is common among women of child-bearing age, with an estimated prevalence of 25% (1,2). Pregnant women were not included in the clinical development program; however, the indicated population is predominantly women, many of whom are of childbearing age. The population of pregnant women treated with eptinezumab is therefore one which warrants further characterization, as effects on the woman and the fetus after exposure in utero are unknown.

The objective of the Post-marketing Pregnancy Program is to collect information and assess the potential risk of use of eptinezumab during pregnancy. The potential increase in the risks of adverse maternal, fetal, and infant outcomes will be evaluated, including risks of birth defects, other adverse pregnancy outcomes (e.g. pre-eclampsia) and postnatal health of liveborn children up to one year of age among the offspring of women exposed to eptinezumab. Data will be collected on women exposed to eptinezumab during pregnancy and their offspring, as well as data on two comparative groups of eptinezumab-unexposed pregnant women with migraine and their offspring.

References:

- 1 Myint A.A., et al. Special Issues in Managing Migraine in Women: A Review Article. *International Journal of Collaborative Research on Internal Medicine & Public Health*. Vol. 5 No. 6 (2013), 478 – 491
- 2 Lipton R.B., et al. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology*. 2007;68(5): 343-349