Part VI: Summary of the risk management plan

Summary of risk management plan for Aimovig (Erenumab)

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

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

This summary of the RMP for Aimovig 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 Aimovig's RMP.

I. The medicine and what it is used for

Aimovig is authorized for the prophylaxis of migraine in adults who have at least 4 migraine days per month (see SmPC for the full indication). It contains erenumab (a human IgG2 monoclonal antibody) as the active substance and it is given by sc injections.

Further information about the evaluation of Aimovig's benefits can be found in Aimovig's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: http://www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/human/medicines/004447/human_med_002275.jsp.

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

Important risks of Aimovig, together with measures to minimize such risks and the proposed studies for learning more about Aimovig's risks, are outlined below in Table 2.

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 patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

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

II.A List of important risks and missing information

Important risks of Aimovig 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 Aimovig. 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 for Aimovig 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).

Table 1 List of important risks and missing information

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
Missing information	Use in pregnant women (including those at risk of pre-eclampsia) Long-term safety

II.B Summary of important risks

Table 2 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	A comprehensive assessment of CV safety in over 2500 patients in the erenumab clinical Phase II/III program including cardiovascular, cerebrovascular and peripheral vascular AEs, BP assessments and electrocardiograms. The program employed an external, independent Cardiovascular Events Committee to adjudicate the selected CV, cerebrovascular, and peripheral vascular AEs. While patients with recent (i.e., within the last 12 months) cardiovascular events such as MI, stroke, TIA, unstable angina, coronary artery bypass surgery or other revascularization procedures were excluded, patients with risk factors for cardiovascular disease (e.g., diabetes, hypertension, and hyperlipidemia) were allowed to participate. Over 70% of subjects had 1 or more baseline cardiovascular risk factor(s) while approximately 30% of subjects had 2 or more. The summation of this evaluation demonstrated no evidence of a relationship between erenumab and cardiovascular, cerebrovascular, and peripheral vascular events in both individual and aggregate AEs. In the subjects with 2 or more CV risk factors at baseline, the incidence of AEs was slightly higher than in subjects with 0 or 1 CV risk factor at the baseline, but similar to the placebo and across treatment groups.

	No relevant differences were observed between these subgroups in the most frequent AEs or AEs associated with cardiac disorders. Looking at the effect on BP, there was no clinically meaningful difference in either systolic or diastolic BP or in the frequency of increased blood pressure AEs with erenumab versus placebo. A few patients reached a post-baseline systolic BP > 160mmHg and these patients were already hypertensive or pre-hypertensive (defined as systolic BP ≥ 140mmHg or diastolic BP ≥ 90mmHg) at baseline and had medical history of hypertension or other confounding factors. There were no relevant differences in change in CV medication observed between erenumab and placebo.
Risk factors and risk groups	Since this is a potential risk, no attributable increase to erenumab has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimization measures	Routine risk minimization measures- SmPC Section 5.1 (Pharmacodynamic properties) SmPC Section 4.4 (Special warnings and precautions for use) Routine pharmacovigilance activities beyond ADRs reporting and signal detection - None Additional risk minimization measures – None
Additional pharmacovigilance activities	NIS - A Non-Interventional Study to examine patient characteristics and drug utilization patterns in migraine patients treated with prophylactic drugs in the Nordic registries.

Table 3 Missing information: Use in pregnant women (including those at risk of pre-eclampsia)

Risk minimization measures	Routine risk minimization measures- SmPC Section 4.6 (Fertility, pregnancy and lactation) Routine pharmacovigilance activities beyond ADRs reporting and signal detection - Intensive monitoring of pregnancy outcomes Additional risk minimization measures – None
Additional pharmacovigilance activities	NIS - A Non-Interventional Study to examine patient characteristics and drug utilization patterns in migraine patients treated with prophylactic drugs in the Nordic registries.

Table 4 Missing information: Long-term safety

Risk minimization measures	Routine risk minimization measures- None Routine pharmacovigilance activities beyond ADRs reporting and signal detection - None Additional risk minimization measures – None
Additional pharmacovigilance activities	20120178 – A Phase 2, Randomized, Double-blind, Placebo controlled Study to Evaluate the Efficacy and Safety of AMG 334 in Migraine Prevention. This study includes a 5-year extension for long-term safety data collection.

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 authorization or specific obligation of Aimovig.

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

Table 5 Other studies in the post-authorization development plan

Study short name: NIS (Non-Interventional Study)	**Rationale and study objectives:** There is a theoretical concern that inhibition of CGRP effect may result in lack of compensatory vasodilation, particularly in the context of the coronary circulation during ischemia-related diseases/conditions. The precise extent of the role played by the canonical CGRP receptor in mediating vasodilatory mechanisms remains unknown as CGRP binds to several other receptors, such as the amylin 1 receptor to which it binds with similar potency as amylin and erenumab selectively binds to the CGRP receptor. Furthermore, multiple pathways and mediators are involved in vasodilation (e.g. nitric oxide, substance P, neurokinins), and it is therefore not exactly clear, what effects, if any, there may be from inhibiting the CGRP pathway alone. In addition, CGRP among other factors plays an important role in maintaining normal fetoplacental development, fetal survival, and vascular adaptations during pregnancy. Hence, there is a theoretical concern that inhibition of CGRP effects could have adverse effects on fetoplacental development for pregnant women. This NIS will characterize the population treated with erenumab in the Nordic countries. This data together with the evaluation of CV adverse events from ongoing studies combined with AEs from the post-marketing setting will provide information on the appropriateness of conducting further post-marketing studies to assess the CV safety in patients treated with erenumab in the real-world setting. The NIS aims to estimate: • Number of migraine patients prescribed with a migraine prophylactic drug (with and without CV history) • Number of pregnant migraine patients prescribed with erenumab and other prophylactic treatments • Pattern of erenumab and possible comparator utilization (prescriber, pattern of use, length of treatment, switching) • General characteristics and clinical features of migraine patients prescribed prophylactic drug • As exploratory: rates of CV events
Study short name: 20120178 - Long-term safety follow-up extension study	**Rationale and study objectives:** Migraine prophylaxis is an area of a large unmet medical need, with insufficient efficacy and poor tolerability being common issues. The primary objective of study 20120178, was to evaluate the effect of erenumab on the change from baseline in monthly migraine days compared to placebo at the end of the 3-month double-blind treatment phase in subjects with episodic migraine. An exploratory objective includes evaluation of the long-term safety and tolerability of erenumab for up to 268 weeks of treatment.