Teva Pharma AG

Swiss Summary of EU RISK MANAGEMENT PLAN V1.4

AJOVY® (Fremanezumab)

Disclaimer: 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 minimise them.

The RMP summary of AJOVY® 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 AJOVY® in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Teva Pharma AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Ajovy.

Basel, 18. Dezember 2019

Active substance(s) (INN or common name):	Fremanezumab
Pharmaco-therapeutic group (ATC Code):	N02CX09
Name of Marketing Authorisation Holder or Applicant:	Teva Pharma AG Kirschgartenstrasse 14 4051 Basel
Number of medicinal products to which this RMP refers:	1 product
Product(s) concerned (brand name(s)):	AJOVY®
Date of updated RMP Summary sign off:	18. Dezember 2019
Local Registered Pharmacovigilance Responsible Person:	Alexandra Weigel Sr Pharmacovigilance Manager, Local Safety Officer Switzerland
Authorised signature:	 iA Sarah Vogel, Pharmacovigilance Officer

Summary of Risk Management Plan for AJOVY (fremanezumab)

This is a summary of the risk management plan (RMP) for AJOVY (herein after also referred to as fremanezumab). The RMP details important risks of AJOVY, how these risks can be minimised, and how more information will be obtained about AJOVY´s risks and uncertainties (missing information).

AJOVY's Summary of Product Characteristics (SmPC) and its Package Leaflet (PL) give essential information to healthcare professionals and patients on how AJOVY should be used.

This summary of the RMP for AJOVY 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 AJOVY´s RMP.

I. The Medicine and What It is used for

AJOVY is authorised for prophylaxis of migraine in adults who have at least 4 migraine days per month (see "Arzneimittelinformation / Information sur le médicament" for the full indication). It contains fremanezumab as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of AJOVY's benefits can be found in AJOVY'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

Important risks of AJOVY, together with measures to minimise such risks and the proposed studies for learning more about AJOVY'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 PL 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, including Periodic Safety Updated Report (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 AJOVY is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of AJOVY 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 AJOVY. 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).

Table1: Summary of Safety Concerns

List of important risks and missing information	
Important identified risks	• None
Important potential risks	• Severe hypersensitivity reactions • Unfavourable cardiovascular outcomes in patients with preexisting myocardial infarction, cerebrovascular accident, transient ischemic attack, angina unstable, and hypertension
Missing information	• Long-term safety • Use in pregnant women (including those at risk of pre-eclampsia)

II.B Summary of Important Risks

Table 2: Summary of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Important Identified Risks: None	
Important Potential Risk: Severe hypersensitivity reactions	
Evidence for linking the risk to the medicine	Severe hypersensitivity reactions are theoretically possible with any injected protein. Mild and moderate drug hypersensitivity events were observed in the clinical development programme. However, it cannot be excluded that events with severe intensity may occur in the future.
Risk factors and risk groups	Patients with known hypersensitivity to the active substance.
Risk minimisation measures	<u>Routine risk minimisation measures</u> • Arzneimittelinformation / Information sur le médicament Sektion Kontraindikationen / Contre-indications as well as Warnhinweise und Vorsichtsmassnahmen / Mises en garde et précautions • Medicinal product subject to restricted medical prescription
Important Potential Risk: Unfavourable cardiovascular outcomes in patients with pre-existing myocardial infarction, cerebrovascular accident, transient ischemic attack, angina unstable, and hypertension	
Evidence for linking the risk to the medicine	Due to its mechanism of action CGRP inhibitors are considered as having a theoretical potential to increase the risk for hypertension/ hypertensive crisis, cardiovascular and cerebrovascular disease, as well as for peripheral arterial disorder. Patients with a history of significant cardiovascular

	and cerebrovascular disease, as well as patients with a history of thromboembolic events had been excluded from trial participation. Due to the clinical trial exclusion criteria limited data are available in this patient group. Based on the data on cardiovascular safety in clinical studies there is no clear trend or signal that suggests an increased risk of cardiac disorders in patients with fremanezumab. In clinical studies the safety profile of fremanezumab was comparable across age groups without specific safety signals for patients with cardiovascular risk factors.
Risk factors and risk groups	Unknown
Risk minimisation measures	Routine risk minimisation measures • Arzneimittelinformation / Information sur le médicament Sektion Warnhinweise und Vorsichtsmassnahmen / Mises en garde et précautions • Patienteninformation / Informations destinées aux patients section Wann ist bei der Anwendung von AJOVY Vorsicht geboten? / Quelles sont les précautions à observer lors de la prise d'AJOVY? • Medicinal product subject to restricted medical prescription
Additional pharmacovigilance activities	• A Long-Term Observational Study to Evaluate the Safety, Including Cardiovascular Safety, of Fremanezumab in Patients with Migraine in Routine Clinical Practice
Missing information: Long-term safety	
Risk minimisation measures	Routine risk minimisation measures • Medicinal product subject to restricted medical prescription
Additional pharmacovigilance activities	• A Multicenter, Randomized, Double-Blind, Parallel-Group Study Evaluating the Long-Term Safety, Tolerability, and Efficacy of Subcutaneous Administration of TEV-48125 for the Preventive Treatment of Migraine (Study number TV48125-CNS-30051) • A Long-Term Observational Study to Evaluate the Safety, Including Cardiovascular Safety, of Fremanezumab in Patients with Migraine in Routine Clinical Practice
Missing information: Use in pregnant women (including those at risk of pre-eclampsia)	
Risk minimisation measures	Routine risk minimisation measures • Arzneimittelinformation / Information sur le médicament Sektion Schwangerschaft/Stillzeit / Grossesse/Allaitement • Patienteninformation / Informations destinées aux patients section Darf AJOVY während einer Schwangerschaft oder in der Stillzeit angewendet werden? / AJOVY peut-il être pris pendant la grossesse ou l'allaitement? • Medicinal product subject to restricted medical prescription
Additional pharmacovigilance activities	• A post authorization safety study for assessment of pregnancy outcomes in patients treated with fremanezumab

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 fremanezumab.

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

Study name	Purpose of the study
A Multicenter, Randomized, Double-Blind, Parallel-Group Study Evaluating the Long- Term Safety, Tolerability, and Efficacy of Subcutaneous Administration of TEV- 48125 for the Preventive Treatment of Migraine (Study number TV48125-CNS- 30051)	The primary objective of the study is to evaluate the long-term safety and tolerability of subcutaneous (sc) fremanezumab in the preventive treatment of migraine.
A post authorization safety study for assessment of pregnancy outcomes in patients treated with fremanezumab	The objectives of this study are to examine pregnant women exposed to fremanezumab during pregnancy and to evaluate: Primary objective: • pregnancy outcomes of major birth defects Secondary objectives: • pre-eclampsia/ eclampsia during pregnancy • maternal and fetal outcomes, including pre-term birth, spontaneous abortions, and stillbirth
A Long-Term Observational Study to Evaluate the Safety, Including Cardiovascular Safety, of Fremanezumab in Patients with Migraine in Routine Clinical Practice	The study is intended to investigate the long-term safety profile (including cardiovascular safety) of fremanezumab in patients with migraine in a real-world clinical practice setting. The primary objectives of this study are the following: • To evaluate the long-term safety of fremanezumab in all patients with migraine (Cohort 1) • To evaluate the safety of fremanezumab in the subset of cardiovascular-compromised patients (both patients with a history of major cardiovascular disease and/or hypertension, as well as those who currently have major cardiovascular disease and/or hypertension) with migraine with regard to cardiovascular events, including development or worsening of hypertension, major adverse cardiovascular events (MACE; including myocardial infarction [MI], stroke, sudden cardiac death, and unstable angina), and heart failure (Cohort 2)