Active substance:	**Perampanel**
Product(s) concerned (brand name(s)):	**Fycompa®** film-coated tablets / oral suspension
MAH/Applicant name:	Eisai Pharma AG
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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 minimise them.

The RMP summary of Fycompa is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the local product information ("Arzneimittelinformation / Information sur le médicament") approved and published in Switzerland, eg, 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 Fycopma in Switzerland is the local product information ("Arzneimittelinformation / Information sur le médicament") (see www.swissmedic.ch) approved and authorized by Swissmedic. Eisai Pharma AG (Eisai) is fully responsible for the accuracy and correctness of the content of the published summary RMP of Fycompa.

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

I The Medicine and What it is Used for

Fycompa is authorised (CH) for the adjunctive treatment of partial onset (focal) seizures (POS) with or without secondarily generalised seizures in adults and children from 4 years of age with epilepsy and for the adjunctive treatment of primary generalised tonic-clonic (PGTC) seizures in adults and children from 7 years of age with idiopathic generalised epilepsy (see local product information for the full indication). It contains perampanel as the active substance and it is given orally as a film-coated tablet or as a suspension.

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

Important risks of Fycompa, together with measures to minimise such risks and the proposed studies for learning more about Fycompa'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 local product information 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 (eg, 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 Period Safety Update 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 Fycompa is not yet available, it is listed under ‘missing information’ below.

II.A List of Important Risks and Missing Information

Important risks of Fycompa 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 Fycompa. 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 (eg, on the long-term use of the medicine).

Public Summary of the Risk Management Plan

1 Overview of disease epidemiology

The incidence of epilepsy in the overall population in developed countries: 40 and 70 per 100,000 persons per year and >120/100,000 per year in resource-poor countries. Incidence is usually higher in younger children (0 to 10 years) and in older people (after 65 years). The incidence of epilepsy is highest in the first year of life and declines to adult levels by the end of the first decade. In the paediatric population, the incidence of specific seizure types and epilepsy syndromes in children is not well documented; only about 1/3 of children with epilepsy can be assigned to a specific epilepsy syndrome. Worldwide, at least 50 million people are estimated to have epilepsy. The prevalence of epilepsy varies substantially between developed and developing countries, with an estimate of 4 to 7 per 1000 persons in the developed countries versus 5 to 74 per 1000 persons in developing countries. Prevalence may vary over time. The absolute difference in gender-specific prevalence is minimal. No statistically significant differences in incidence among race were noted.

2 Summary of treatment benefits

Fycompa is authorised in Switzerland for the adjunctive treatment of partial onset (focal) seizures (POS) with or without secondarily generalised seizures in adults and children from 4 years of age with epilepsy and for the adjunctive treatment of primary generalised tonic-clonic (PGTC) seizures in adults and children from 7 years of age with idiopathic generalised epilepsy (see the local product information for the full indication). It contains perampanel as the active substance and it is given orally as a film-coated tablet or as a suspension.

It is estimated that there have been over approximately 45 million patient-days of exposure from product launch to June 2018.

3 Unknowns relating to treatment benefits

Not addressed in the RMP.

4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Aggression	There is a potential risk of behavioural abnormalities affecting interpersonal relationships	Patients should be monitored for signs of significant psychiatric disorders and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should they emerge.
Interaction with levonorgestrel-containing contraceptives, and unintended pregnancy exposures	Fycompa was shown to decrease the levonorgestrel exposure in healthy women who received 12 mg for 21 days concomitantly with a combined oral contraceptive. This was not observed in women receiving Fycompa 4 or 8 mg/day.	The possibility of decreased efficacy of contraceptives containing levonorgestrel should be considered for women taking perampanel 12 mg/day and an additional non-hormonal form of contraception is to be used

Risk	What is known	Preventability
Suicidality	There have been serious reports of suicidality in clinical studies	Patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Hepatic disorders (excluding hepatic disorders induced by SCARs)	Some of the metabolites identified for perampanel appear likely to be formed via reactive intermediates. Idiosyncratic toxicities, including hepatotoxicity, have been associated with the mechanism in which reactive intermediates covalently bind to proteins, especially if reduced glutathione (GSH) levels have become depleted. Covalent binding has been observed in preclinical studies of perampanel, at exposures much higher than clinical exposures. There is evidence that idiosyncratic toxicities are rare when the clinical daily dose of drug is given at daily doses ≤10 mg.

Missing information

Risk	What is known
Impact on cognition and growth in the paediatric population	There are limited amounts of long-term data in the paediatric population.
Use in human pregnancy and lactation	There has been limited exposure to perampanel in patients who have become pregnant. Perampanel is not recommended in women of childbearing potential not using contraception unless clearly necessary.

5. Summary of risk minimisation measures by safety concern

All medicines have product information which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the local package leaflet. The measures in these documents are known as routine risk minimisation measures.

The local product information and the package leaflet for perampanel can be found on www.swissmedicinfo.ch.

These additional risk minimisation measures are for the following risks:

Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Important Identified Risks	
Aggression	Routine risk communication is described in the local product information. Routine risk minimisation activities recommending specific clinical measures to address the risk: The recommendations to reduce the dose of perampanel if symptoms of aggression occur and to discontinue treatment immediately if the symptoms are severe are included in the local product information. Other routine risk minimisation measures beyond the local product information: Questionnaires.
Interaction With Levonorgestrel-Containing Contraceptives, and Unintended Pregnancy Exposures	Routine risk communication is described in the local product information. Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable Other routine risk minimisation measures beyond the local product information: None.
Suicidality	Routine risk communication is described in the local product information. Routine risk minimisation activities recommending specific clinical measures to address the risk: The recommendations to monitor for signs of suicidal ideation and behaviours, and to consider appropriate treatment, are included in the local product information. Other routine risk minimisation measures beyond the local product information: Questionnaires.
Important Potential Risks	
Hepatic disorders (excluding hepatic disorders induced by SCARs)	Routine risk communication is described in the local product information. Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable Other routine risk minimisation measures beyond the Product Information: None.
Missing Information	
Impact on cognition and growth in the paediatric population	Routine risk communication is described in the local product information. Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable Other routine risk minimisation measures beyond the local product information: Questionnaires.
Use in human pregnancy and lactation	Routine risk communication is described in the local product information. Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable Other routine risk minimisation measures beyond the local product information: Questionnaires.

SCARs = severe cutaneous adverse reactions

6 Planned post authorisation development plan

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