EUROPEAN UNION RISK MANAGEMENT PLAN FOR FYCOMPA (PERAMPANEL)

RMP Version to be Assessed as Part of This Application:

Risk Management Plan (RMP) version number:	4.5
Data lock point of this RMP:	22 Jul 2019
Date of final sign-off:	13 May 2020
Rationale for submitting an updated RMP:	Removed hypersensitivity to perampanel from special populations not included in the clinical development programme as hypersensitivity is not a population under missing information. Clarified report date previously listed for Study E2007-J081-233 was an interim report date and added final report date. Removed the following safety concerns classified as missing information from the list of safety concerns: use in patients with cardiovascular disease, hypertension, congestive heart failure, history of myocardial infarction or any evidence of risk factors for QT prolongation, use in patients with a history of psychotic disorder or suicidal behaviour in the previous 2 years, use in patients with a history of drug or alcohol dependency, use in patients who are taking vigabatrin, use in patients with hepatic insufficiency whether related to concomitant medications or underlying liver disease, use in patients with clinically significant renal or respiratory disease, and use in the elderly with epilepsy, with particular monitoring of dizziness, balance disorders and falls.

SUMMARY OF SIGNIFICANT CHANGES IN THIS RMP:

Part/Module/Annex	Major Change(s)	Version Number and Date
Part II: Safety Specification		
Part II: Module SIII Clinical Trial Exposure	Error correction in table of Total Subject Exposure to Perampanel in Clinical Trials by Indication	4.5, 13 May 2020
Part II: Module SIV Populations Not Studied in Clinical Trials	Removed hypersensitivity to perampanel from special populations not included in the clinical development programme as hypersensitivity is not a population under missing information. Removed exclusion criterion in pivotal studies across the development program for evidence of significant active hepatic disease and precauction for mild/moderate hepatic disease as this safety concerns previously classified as missing information has been removed from the list of safety concerns.	4.5, 13 May 2020
Part II: Module SVII: Identified and Potential Risks		
SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP	The following safety concerns classified as missing information are removed from the list of safety concerns: • Use in patients with cardiovascular disease, hypertension, congestive heart failure, history of myocardial infarction or any evidence of risk factors for QT prolongation • Use in patients with a history of psychotic disorder or suicidal behaviour in the previous 2 years • Use in patients with a history of drug or alcohol dependency • Use in patients who are taking vigabatrin • Use in patients with hepatic insufficiency whether related to concomitant medications or underlying liver disease • Use in patients with clinically significant renal or respiratory disease • Use in the elderly with epilepsy, with particular monitoring of dizziness, balance disorders and falls	4.5, 13 May 2020

Part/Module/Annex	Major Change(s)	Version Number and Date
SVII.3.1 Details of Important Identified Risks, Important Potential Risks and Missing Information	Removed tables that detailed data that are no longer classified as missing information from the list of safety concerns	4.5, 13 May 2020
Part II: Module SVIII Summary of the Safety Concerns	SVIII Table 17 Removed items that are no longer classified as missing information from the list of safety concerns	4.5, 13 May 2020
Part V: Risk Minimisation Measures (Including Evaluation of The Effectiveness of Risk Minimisation Activities)		
Part V.1: Routine Risk Minimisation Measures	Removed items that are no longer classified as missing information from description of routine risk minimisation measures by safety concern	4.5, 13 May 2020
Part V.3: Summary of Risk Minimisation Measures	Removed items that are no longer classified as missing information from the summary table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety	4.5, 13 May 2020
Part VI: Summary of the Risk Management Plan		
Part VI.II.A: List of Important Risks and Missing Information	Removed items from the list of important risks and missing information that are no longer classified as missing information	4.5, 13 May 2020
Part VI.II.B: Summary of Important Risks	Removed items from the summary of important identified risks that are no longer classified as missing information	4.5, 13 May 2020
Part VII: Annexes	Clarified interim data report and final report dates for Study E2007-J081-233.	4.5, 13 May 2020

Other RMP versions under evaluation:	Not applicable
RMP version number:	Not applicable
Submitted on:	Not applicable
Procedure number:	Not applicable
Details of the currently approved RMP:	
Version number:	4.2
Approved with procedure:	EMEA/H/C/002434/X/0025

Date of approval (opinion date):	19 Sep 2016
Qualified Person for Pharmacovigilance (QPPV) Name:	Angela Schmidt-Mertens EU QPPV and General Safety Officer International Pharmacovigilance Eisai GmbH Lyoner Straße 36 60528 Frankfurt Germany
QPPV oversight declaration	The content of this RMP has been reviewed and approved by Eisai GmbH's QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition of Term
ABT	aminobenzotriazole
AE	adverse event
AED	antiepileptic drugs
ALT	alanine aminotransaminase
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AST	aspartate aminotransaminase
ATC	Anatomical Therapeutic Classification
CHMP	Committee for Medicinal Products for Human Use
CNS	central nervous system
CSR	clinical study report
CYP	cytochrome
DRESS	drug reaction with eosinophilia and systemic symptoms
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessments Report
EU	European Union
EURAP	European and International Registry of Anti-epileptic drugs in Pregnancy
GVP	Good Pharmacovigilance Practice
hERG	human ether-a-go-go related gene
IC_{50}	half maximal inhibitory concentration
IGF-1	insulin growth factor-1
INN	International Non-proprietary Name
NMDA	N-Methyl-D-aspartic acid
NRU	neutral red uptake
PASS	postauthorisation safety study
PD	pharmacodynamic(s)
PGTC	primary generalised tonic-clonic
PIP	Paediatric Investigational Plan
PK	pharmacokinetic(s)
PL	Package Leaflet
POS	partial-onset seizures
PSUR	Periodic Safety Update Report
PV	pharmacovigilance

Abbreviation	Definition of Term
QPPV	European Qualified Person for Pharmacovigilance
QT_c	corrected QT interval
RMP	Risk Management Plan
RR	relative risk
SAE	serious adverse event
SCAR	severe cutaneous adverse reaction
SmPC	Summary of Product Characteristics
SMR	standardised mortality ratio
SUDEP	sudden unexpected death in epilepsy
TEAE	treatment emergent adverse event

PART I PRODUCT(S) OVERVIEW

Table 1 Product Overview

Active substance(s) (International non-proprietary name [INN] or common name)	perampanel
Pharmacotherapeutic group(s) (Anatomical Therapeutic Classification [ATC] Code)	Antiepileptic N03AX22
Marketing Authorisation Holder	Eisai GmbH
Medicinal products to which this Risk Management Plan (RMP) refers	1
Invented name(s) in the European Economic Area (EEA)	Fycompa
Marketing authorisation procedure	Centralised
Brief description of the product	
Chemical class	Perampanel is a selective noncompetitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptor antagonist.
Summary of mode of action	Perampanel binds at a still-unidentified allosteric site distinct from the AMPA binding site.
Important information about its composition	Not applicable.
Hyperlink to the Product Information	The proposed Summary of Product Characteristics (SmPC) is included in Module 1.3.1.
Indication(s) in the EEA Current (if applicable)	Fycompa (perampanel) is indicated for the adjunctive treatment of partial-onset seizures (POS) with or without secondarily generalised seizures in adult and adolescent patients from 12 years of age with epilepsy. Fycompa (perampanel) is indicated for the adjunctive treatment of primary generalised tonic-clonic (PGTC) seizures in adult and adolescent patients from 12 years of age with idiopathic generalised epilepsy.

Table 1 Product Overview

Indication(s) in the EEA (continued) Proposed (if applicable)	Partial onset (focal) seizures with or without secondary generalisation • Fycompa is indicated for adjunctive treatment in adult and adolescent patients from 12 years of age with epilepsy. • Fycompa is indicated for the adjunctive treatment in paediatric patients from 2 to 11 years of age with epilepsy. Primary Generalised Tonic-Clonic Seizures • Fycompa is indicated for adjunctive treatment in adult and adolescent patients from 12 years of age with idiopathic generalised epilepsy. • Fycompa is indicated for adjunctive treatment in paediatric patients from 2 to 11 years of age with idiopathic generalised epilepsy.
Dosage in the EEA Current (if applicable)	Fycompa film-coated tablets: *Adults and adolescents* Fycompa must be titrated, according to individual patient response, in order to optimise the balance between efficacy and tolerability. Perampanel should be taken orally once daily at bedtime. *Partial-Onset Seizures* Perampanel at doses of 4 mg/day to 12 mg/day has been shown to be effective therapy in POS. Treatment with Fycompa should be initiated with a dose of 2 mg/day. The dose may be increased based on clinical response and tolerability by increments of 2 mg (either weekly or every 2 weeks as per half-life considerations described below) to a maintenance dose of 4 mg/day to 8 mg/day. Depending upon individual clinical response and tolerability at a dose of 8 mg/day, the dose may be increased by increments of 2 mg/day to 12 mg/day. Patients who are taking concomitant medicinal products that do not shorten the half-life of perampanel (see Section 4.5 of the SmPC) should be titrated no more frequently than at 2-week intervals. Patients who are taking concomitant medicinal products that shorten the half-life of perampanel (see Section 4.5 of the SmPC) should be titrated no more frequently than at 1-week intervals.

Table 1 Product Overview

Dosage in the EEA (continued) Current (if applicable) (continued)	Fycompa film-coated tablets (continued): *Primary Generalised Tonic-Clonic Seizures* Perampanel at a dose up to 8 mg/day has been shown to be effective in primary generalised tonic-clonic seizures. Treatment with Fycompa should be initiated at a dose of 2 mg/day. The dose may be increased based on clinical response and tolerability by increments of 2 mg (either weekly or every 2 weeks, as per half-life considerations described below) to a maintenance dose of up to 8 mg/day. Depending upon individual clinical response and tolerability at a dose of 8 mg/day, the dose may be increased up to 12 mg/day, which may be effective in some patients (see Section 4.4 of the SmPC). Patients who are taking concomitant medicinal products that do not shorten the half-life of perampanel (see Section 4.5 of the SmPC) should be titrated no more frequently than at 2-week intervals. Patients who are taking concomitant medicinal products that shorten the half-life of perampanel (see Section 4.5 of the SmPC) should be titrated no more frequently than at 1-week intervals. Fycompa 0.5 mg/ml oral suspension: *Adults and adolescents* Fycompa must be titrated, according to individual patient response, in order to optimise the balance between efficacy and tolerability. Perampanel suspension should be taken orally once daily at bedtime. It may be taken with or without food, but preferably always under the same conditions. Switching between the tablet and suspension formulation should be done with caution (see Section 5.2 of the SmPC). *Partial-Onset Seizures* Perampanel at doses of 4 mg/day to 12 mg/day has been shown to be effective therapy in partial onset seizures. Treatment with Fycompa should be initiated with a dose of 2 mg/day (4 ml/day). The dose may be increased based on clinical response and tolerability by increments of 2 mg (4 ml) (either weekly or every 2 weeks as per half-life considerations described below) to a maintenance dose of 4 mg/day (8 ml/day) to 8 mg/day (16 ml/day). Depending upon individual clinical response and tolerability at a dose of 8 mg/day (16 ml/day), the dose may be increased by increments of 2 mg/day (4 ml/day) to 12 mg/day (24 ml/day). Patients who are taking concomitant medicinal products that do not shorten the half-life of perampanel (see Section 4.5 of the SmPC) should be titrated no more frequently than at 2-week intervals. Patients who are taking concomitant medicinal products that shorten the half-life of perampanel (see Section 4.5 of the SmPC) should be titrated no more frequently than at 1-week intervals.

Table 1 Product Overview

Dosage in the EEA (continued) Current (if applicable) (continued)	Fycompa 0.5 mg/ml oral suspension (continued): *Primary Generalised Tonic-Clonic Seizures* Perampanel at a dose up to 8 mg/day has been shown to be effective in primary generalised tonic-clonic seizures. Treatment with Fycompa should be initiated at a dose of 2 mg/day (4 ml/day). The dose may be increased based on clinical response and tolerability by increments of 2 mg (4 ml/day) (either weekly or every 2 weeks, as per half-life considerations described below) to a maintenance dose of up to 8 mg/day (16 ml/day). Depending upon individual clinical response and tolerability at a dose of 8 mg/day (16 ml/day), the dose may be increased up to 12 mg/day (24 ml/day), which may be effective in some patients (see Section 4.4 of the SmPC). Patients who are taking concomitant medicinal products that do not shorten the half-life of perampanel (see Section 4.5 of the SmPC) should be titrated no more frequently than at 2-week intervals. Patients who are taking concomitant medicinal products that shorten the half-life of perampanel (see Section 4.5 of the SmPC) should be titrated no more frequently than at 1-week intervals.
Proposed (if applicable)	Fycompa film-coated tablets: *Adults, adolescents age ≥12 years and children age 2 to 11 years* Fycompa must be titrated, according to individual patient response, in order to optimise the balance between efficacy and tolerability. Perampanel should be taken orally once daily at bedtime. *Partial-Onset Seizures* Perampanel at doses of 4 mg/day to 12 mg/day has been shown to be effective therapy in POS. Treatment with Fycompa should be initiated with a dose of 2 mg/day. The dose may be increased based on clinical response and tolerability by increments of 2 mg (either weekly or every 2 weeks as per half-life considerations described below) to a maintenance dose of 4 mg/day to 8 mg/day. Depending upon individual clinical response and tolerability at a dose of 8 mg/day, the dose may be increased by increments of 2 mg/day to 12 mg/day. Patients who are taking concomitant medicinal products that do not shorten the half-life of perampanel (see Section 4.5 of the SmPC) should be titrated no more frequently than at 2-week intervals. Patients who are taking concomitant medicinal products that shorten the half-life of perampanel (see Section 4.5 of the SmPC) should be titrated no more frequently than at 1-week intervals.

Table 1 Product Overview

Dosage in the EEA (continued) Proposed (if applicable) (continued)	Fycompa film-coated tablets (continued): *Primary Generalised Tonic-Clonic Seizures* Perampanel at a dose up to 8 mg/day has been shown to be effective in primary generalised tonic-clonic seizures. Treatment with Fycompa should be initiated at a dose of 2 mg/day. The dose may be increased based on clinical response and tolerability by increments of 2 mg (either weekly or every 2 weeks, as per half-life considerations described below) to a maintenance dose of up to 8 mg/day. Depending upon individual clinical response and tolerability at a dose of 8 mg/day, the dose may be increased up to 12 mg/day, which may be effective in some patients (see Section 4.4 of the SmPC). Patients who are taking concomitant medicinal products that do not shorten the half-life of perampanel (see Section 4.5 of the SmPC) should be titrated no more frequently than at 2-week intervals. Patients who are taking concomitant medicinal products that shorten the half-life of perampanel (see Section 4.5 of the SmPC) should be titrated no more frequently than at 1-week intervals. Fycompa 0.5 mg/ml oral suspension: *Adults, adolescents age ≥12 years and children age 2 to 11 years* Fycompa must be titrated, according to individual patient response, in order to optimise the balance between efficacy and tolerability. Perampanel suspension should be taken orally once daily at bedtime. It may be taken with or without food, but preferably always under the same conditions. Switching between the tablet and suspension formulation should be done with caution (see Section 5.2 of the SmPC). *Partial-Onset Seizures* Perampanel at doses of 4 mg/day to 12 mg/day has been shown to be effective therapy in POS. Treatment with Fycompa should be initiated with a dose of 2 mg/day (4 ml/day). The dose may be increased based on clinical response and tolerability by increments of 2 mg (4 ml) (either weekly or every 2 weeks as per half-life considerations described below) to a maintenance dose of 4 mg/day (8 ml/day) to 8 mg/day (16 ml/day). Depending upon individual clinical response and tolerability at a dose of 8 mg/day (16 ml/day) the dose may be increased by increments of 2 mg/day (4 ml/day) to 12 mg/day (24 ml/day). Patients who are taking concomitant medicinal products that do not shorten the half-life of perampanel (see Section 4.5 of the SmPC) should be titrated no more frequently than at 2-week intervals. Patients who are taking concomitant medicinal products that shorten the half-life of perampanel (see Section 4.5 of the SmPC) should be titrated no more frequently than at 1-week intervals.

Table 1 Product Overview

Dosage in the EEA (continued) Proposed (if applicable) (continued)	Fycompa 0.5 mg/ml oral suspension (continued): *Primary Generalised Tonic-Clonic Seizures* Perampanel at a dose up to 8 mg/day has been shown to be effective in primary generalised tonic-clonic seizures. Treatment with Fycompa should be initiated at a dose of 2 mg/day (4 ml/day). The dose may be increased based on clinical response and tolerability by increments of 2 mg (4 ml/day) (either weekly or every 2 weeks, as per half-life considerations described below) to a maintenance dose of up to 8 mg/day (16 ml/day). Depending upon individual clinical response and tolerability at a dose of 8 mg/day (16 ml/day), the dose may be increased up to 12 mg/day (24 ml/day), which may be effective in some patients (see Section 4.4 of the SmPC). Patients who are taking concomitant medicinal products that do not shorten the half-life of perampanel (see Section 4.5 of the SmPC) should be titrated no more frequently than at 2-week intervals. Patients who are taking concomitant medicinal products that shorten the half-life of perampanel (see Section 4.5 of the SmPC) should be titrated no more frequently than at 1-week intervals.
Pharmaceutical form(s) and strengths Current (if applicable)	Perampanel tablets are round, biconvex, film-coated tablets containing 2 mg (orange), 4 mg (red), 6 mg (pink), 8 mg (purple), 10 mg (green), and 12 mg (blue) of perampanel. Perampanel oral suspension is a white to off-white suspension. Each ml of oral suspension contains 0.5 mg perampanel.
Proposed (if applicable)	None
Is/will the product be subject to additional monitoring in the European Union (EU)?	No

PART II SAFETY SPECIFICATION

Part II Module SI - Epidemiology of the Indication(s) and Target Population(s)

Table 2 Summary of Epidemiology of Partial-Onset Seizures and Primary Generalised Tonic-Clonic Seizures

Incidence	Incidence of epilepsy in the overall population: Developed countries: 40 and 70 per 100,000 persons per year (Sander and Shorvon, 1996) Usually higher in younger children (0 to 10 years) and in older people (after 65 years) (Duncan, et al. 2006; Forsgren, et al. 2005; Sander, 2003; MacDonald, et al. 2000). • Resource-poor countries: >120/100,000 per year (de Boer, et al. 2008) • In North America, age-adjusted incidence: 16 to 51 per 100,000 person-years (Benn, et al. 2008; Hauser, et al. 1993) • In South America, rural Chile age-adjusted incidence: 111 per 100,000 person-years (Lavados, et al. 1992). • European studies age-adjusted incidence: 26 (Norway [de Graaf, 1974]) to 47 (England [MacDonald, et al. 2000]) per 100,000 person years • In Asia, India age-adjusted incidence: 35 per 100,000 person-years (Mani, et al. 1998) • In Africa, age-adjusted incidence: 43 (Ethiopia [Rwiza, et al. 1992] to 51 (Tanzania [Tekle-Haimanot, et al. 1997]) per 100,000 person-years Incidence of epilepsy 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 (Camfield and Camfield, 2015). Therefore, the following epidemiology data are reported for paediatric epilepsy (with specific data for partial-onset seizures or primary generalised tonic-clonic seizures reported if available): • Overall incidence: 41 to 187/100,000 (Camfield and Camfield, 2015) o Incidence in underdeveloped countries, particularly rural areas, is higher than in developed countries o There was a slight, but consistent, predominance of focal seizures (53% to 68%) compared with generalised seizures (including absence seizures) (23% to 43%) • In developed countries: 33 to 82 in 100,000 persons per year (Sokka, et al. 2017) • Standardised incidence in Europe: 24 to 82/100,000 population/year (Behr, et al. 2016) • In Finland: 38 per 100,000 (Sokka, et al. 2017) • In Germany, the total age-adjusted annual incidence rate of epilepsies and epileptic syndromes in children and adolescents (1 month to <15 years of age) was 60 per 100,000 with the highest incidence in the first year of life (146/100,000). Focal

Table 2 Summary of Epidemiology of Partial-Onset Seizures and Primary Generalised Tonic-Clonic Seizures

	epilepsies or epileptic syndromes (58%; incidence rate, 35/100,000) were more common than generalised seizures (39%; incidence rate, 24/100,000). The rate of idiopathic (47%; incidence rate, 29/100,000) and symptomatic or cryptogenic epilepsies (50%; incidence rate, 30/100,000) was equal (Freitag, et al. 2001). • In a more recent study in Germany (Goettingen), the incidence of epilepsies in children and adolescents (<16 years) was 97.8 per 100,000 inhabitants (in this age range), ie, approximately 1:1000. Focal epilepsies as a whole (symptomatic and cryptogenic focal epilepsies [38%] as well as benign genetic partial epilepsies [24%]) were more frequent (67%) than generalised epilepsies (22%) (Isenber, et al. 2018). • Standardised incidence in the US: 44 to 162/100,000 population/year (Behr, et al. 2016). • In US (Minnesota), adjusted incidence rate of new onset epilepsy in children: 44.5 cases per 100,000 persons per year (focal: 68%; generalised/bilateral: 23%; others/unknown: 8-9%) (Wirrell, et al. 2011).
Prevalence	Prevalence of epilepsy in the overall population: Worldwide, at least 50 million people are estimated to have epilepsy (Leonardi and Ustun. 2002; Meinardi, et al. 2001). More than 80% of those live in developing countries, where the condition remains largely untreated (Koul, et al. 1988). Partial seizures are more prevalent in countries where cysticercosis is prevalent (World Health Organization, 2001). • 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 (Sander and Shorvon, 1996) versus 5 to 74 per 1000 persons in developing countries (Preux and Druet-Cabanc, 2005). Additionally, the median lifetime epilepsy prevalence for developed countries was 5.8 per 1000 (5th–95th percentile range 2.7–12.4) compared to 15.4 per 1000 (4.8–49.6) for rural and 10.3 (2.8-37.7) for urban studies in developing countries. The median prevalence of active epilepsy was 4.9 per 1000 (2.3-10.3) for developed countries and 12.7 per 1000 (3.5-45.5) and 5.9 (3.4–10.2) in rural and urban studies in developing countries (Ngugi, et al. 2010). • Age-adjusted prevalence in studies that used door-to-door survey methodology ranged from 2.2 in India (Koul, et al. 1988) to 41.0 per 1000 in Nigeria (Longe and Osuntokun. 1989). • In the North American studies, the age-adjusted prevalence was 5.0 in New York (Basch, et al. 1997) and 7.1 per 1000 in Mississippi (Haerer, et al. 1986). • In Central and South America, the overall age-adjusted prevalence ranged from 3.7 per 1000 in Argentina (Melcon, et al. 2007) to 22.2 per 1000 in Ecuador (Cruz, et al. 1985).

Table 2 Summary of Epidemiology of Partial-Onset Seizures and Primary Generalised Tonic-Clonic Seizures

	• In Europe, age-adjusted prevalence was low, 2.7 to 3.3 per 1000 in Italy (Onal, et al. 2002; Meneghini, et al. 1991) when compared to a prevalence of 7.0 per 1000 in the European region of Turkey (Wright, et al. 2000). Prevalence of epilepsy in the paediatric population: • The prevalence in paediatrics with epilepsy (aged 0 to 18 years; 3.4-5.8/1000; Waaler, et al. 2000; Beilmann, et al. 1999; Forsgren, et al. 2005) was similar to that reported in the general population (3.3-7.8/1000; Forsgren, et al. 2005) in Europe. Moreover, the prevalence may vary over time based on a registry study in Sweden, where the prevalence increased from 6.2/1000 in 2005 to 8.8/1000 in 2011 (Behr, et al. 2016). • The prevalence of focal versus generalised seizures can vary across studies (number of subjects included in the study) and regions/countries. For example, o Based on electroencephalography examinations, the prevalence rates ranges from 35% to 50% for focal seizures and ranged from 17% to 60% for generalised seizures (Behr, et al. 2016). o In Pakistan, the prevalence of generalised tonic-clonic seizures in paediatric patients with epilepsy was 52.3% (Khan, et al. 2019). In India (single center): 4 to 6 cases per 1000 children; generalised tonic-clonic (70%), simple partial seizure (4%) (Raj, et al. 2017).
Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin	Age: • The incidence of epilepsy is highest in the first year of life and declines to adult levels by the end of the first decade (Aaberg, et al. 2017; Camfield and Camfield, 2015; Freitag, et al. 2001). Aaberg et al. reported the incidence to be declining from 144/100,000 person-years in under 1 year of age, to 61/100,000 person-years in 1 to 4 years of age and 54/100,000 person-years in 5 to 10 years of age; compared to 70/100,000 person-years across all ages (Aaberg, et al. 2017). • After adjusting for age, no significant differences in incidence of epilepsy over time have been noticed (Banerjee, et al. 2009; Lavados, et al. 1992).

	• The prevalance of epilepsy can vary across different countries and with different age-specific populations with a range of 3.4 to 5.8/1000 in paediatric (age 0 to 18 years) studies (Waaler, et al. 2000; Beilmann, et al. 1999), which is similar to the range of 3.3 to 7.8/1000 inhabitants in the general population (Forsgren, et al. 2005) in Europe. • However, in a large registry study, prevalence rates were reported to be age-dependent. In adults, the rates were 55% to 83% for focal seizures, 6% to 32% for generalised seizures, and 8% to 20% for unclassified seizures. In children, these rates were 42% to 60%, 30% to 58%, and 0% to 5%, respectively. (Behr, et al. 2016) • In Pakistan, the prevalence of generalised tonic-clonic seizures in paediatric patients with epilepsy was 52.3% (Khan, et al. 2019). Partial or localisation-related epilepsies account for 20% to 66% of incident epilepsies in population-based studies of all ages (Carroll and Benbadis, 2009; Olafsson, et al. 2005; Annegers, et al. 1999; Tekle-Haimanot, et al. 1997; Olafsson, et al. 1996; Lavados, et al. 1992; Rwiza, et al. 1992; Joensen, 1986; Granieri, et al. 1983). Incidence of partial seizures in people aged less than 60 years is 20 cases per 100,000 person-years and for persons aged 60 to 80 years increases to 80 cases per 100,000 person-years (World Health Organization, 2001). • Most reports show a general trend towards an increase in prevalence during adolescence or early adulthood (Reggio, et al. 1996; Giuliani, et al. 1992; Lavados, et al. 1992; Kogeorgos, et al. 1982). In developed countries, most studies show the prevalence of epilepsy to be stable in the adult age groups and to increase with age after 50 (de Boer, et al. 2008; Gallitto, et al. 2005). In most studies in developing countries, prevalence of epilepsy remains stable in the third to fourth decades and typically drops after the fifth decade of life. In a few studies, prevalence then again increases after age 40 (Reggio, et al. 1996; Lavados, et al. 1992; Kogeorgos, et al. 1982). Gender: Information about gender differences in the incidence and prevalence of epilepsy was reported in 19 and 14 population-based studies, respectively (Forsgren, et al. 2005). Even though quite a few studies reported a higher incidence/prevalence in males than females; these differences between genders are seldom significant (Forsgren, et al. 2005; Hauser, et al. 1993). A majority of studies report higher prevalence in males than females. However, the absolute difference in gender-specific prevalence is minimal. Likewise, in paediatrics with epilepsy, the incidence and prevalence were either comparable or numerically slightly higher in males than females; however, these differences are insignificant (Aaberg, et al. 2017). Race: No statistically significant differences in incidence among non-Hispanic Whites, African Americans, Hispanics, and Asians were noted in a study based on Health Maintenance Organization enrolees and their families in the US, eliminating much of the influence of socioeconomic status

Table 2 Summary of Epidemiology of Partial-Onset Seizures and Primary Generalised Tonic-Clonic Seizures

	(Annegers, et al. 1999). Similarly, a study estimating incidence of epilepsy in an urban community found similar rates in Hispanics, Whites, and African Americans (Benn, et al. 2008). Approximately 20% to 25% of cases of epilepsy are classified as generalised seizures. The National General Practice Study of newly diagnosed epilepsy in the UK found that of 564 incident cases, 29% had primary generalised seizures (Sander, et al. 1990). Like other types of seizures, PGTC seizures are caused by the paroxysmal, uncontrolled discharge of CNS neurons, leading to neurologic dysfunction. This cerebral hyperactivity extends to the entire brain with PGTC seizures, unlike most other types of seizures. PGTC seizures are associated with idiopathic generalised epilepsy and several generalised epilepsy syndromes. The most debilitating seizure type within the generalised epilepsies is the tonic-clonic seizure. Onset of PGTC seizures typically starts in older children, adolescents, and young adults. Because PGTC seizures are associated with an increased risk of injury and death, effective control of these seizures is necessary to reduce epilepsy-related morbidity and mortality.
Risk factors for the disease	Risks of epilepsy include: a) age, with onset of epilepsy most common during early childhood and in the elderly; b) family history; c) head injuries, especially brain penetrating ones; c) stroke and other vascular diseases; d) dementia, which increases the risk of epilepsy in older adults; e) brain infections; f) seizures in childhood (Shorvon, 2011).
The main existing treatment options	Many patients' partial seizures are treated with combinations of AEDs. However, despite the variety of currently marketed AEDs, epilepsy is not totally controlled for over a third of patients. Current treatments also have clinically relevant tolerability issues. Up to a quarter of the patients initially exposed to an AED will have adverse effects severe enough to require drug withdrawal. Thus, new effective and safe treatments are urgently needed.

Natural history of the indicated condition in the population, including mortality and morbidity	Chronic epilepsy patients have an increased risk of premature death (Sander, 2004; Lhatoo, et al. 2001). Symptomatic epilepsy may reduce life expectancy by up to 18 years (Nilsson, et al. 1997). The mortality rate among individuals with epilepsy is 2 to 3 times that of the general population. Most deaths are due to the underlying cause of epilepsy with remainder due to accidents, sudden unexpected death in epilepsy (SUDEP), and suicides. SUDEP occurs with no apparent cause. The annual incidence of SUDEP is 1 in 2500 persons with mild epilepsy and 1 in 250 persons with severe epilepsy (Birbeck and Kalichi, 2004). In a large cohort study of all patients >15 years old, in whom a diagnosis of epilepsy was recorded at discharge from any hospital in Stockholm during 1980 to 1989, a standardised mortality ratio (SMR) of 3.6 (CI: 3.5, 3.7) was estimated (Shackleton, et al. 2002). In a retrospective study of the survival status of outpatients seen in a Dutch epilepsy centre over a 40-year period (38,665 person-years, 404 deaths), the SMR was 3.2 (CI: 2.9, 3.5) (Klenerman, et al. 1993). SMRs for institutionalised populations (ie, patients living in residential epilepsy centers) range between 1.9 and 3.0 (Klenerman, et al. 1993; White, et al. 1979; Henriksen, et al. 1967). • The proportion of deaths due to epilepsy is higher in selected population studies; proportional mortality ratio was 18% to 41% (Shackleton, et al. 1999; Iivanainen and Lehtinen, 1979; Zieliński, 1974; Krohn, 1963) compared with rates within community (1% to 13%) (Gaitatzis, et al. 2004; Olafsson, et al. 1998; Sillanpää, et al. 1998; Harvey, et al. 1993; Hauser, et al. 1980). • Mortality was not increased in Rochester patients with complex partial seizures with or without generalisation (SMR=1.5, n.s.) (Harvey, et al. 1993). In Iceland, idiopathic cases with partial seizures (all types combined) did not have an increased mortality (SMR=1.5; 95% CI: 0.7, 2.8) (Lindsten, et al. 2000). In Sweden, partial seizures were associated with an increased mortality (SMR=2.1; 95% CI: 1.2, 3.6) when all etiologies were considered together (Lindsten, et al. 2000). In most studies, mortality was higher in males with epilepsy than in females (Lindsten, et al. 2000; Harvey, et al. 1993; Hauser and Hesdorrfer, 1990; White, et al. 1979). At all ages, the SMR was increased for people with epilepsy compared to referent populations. Most studies have found an inverse relationship between SMR and age (Tellez-Zenteno, et al. 2007; Harvey, et al. 1993; Hauser, et al. 1980). The highest SMRs are found in children, while decreasing SMRs are found with increasing age. However, the highest excess mortality is found in the elderly (47 per 1000 or 8 times higher than children in people 75 years of age and older) (Birbeck and Kilichi, 2004; Sillanpää, et al. 1998). While patients with refractory primary generalised tonic-clonic seizures represent a minority of the population with epilepsy, they require the overwhelming majority of time, effort, and focus from treating physicians (Laxer, et al. 2014). They also represent the greatest economic and psychosocial burdens. In a crude analysis, generalised tonic-clonic seizure frequency, AED polytherapy, and number of AEDs were associated with an increased risk for SUDEP (Hesdorffer, et al. 2012). Analysis of individual AEDs and

Table 2 Summary of Epidemiology of Partial-Onset Seizures and Primary Generalised Tonic-Clonic Seizures

	of number of AEDs, adjusting for generalised tonic-clonic seizure frequency, revealed no increased risk associated with AEDs as monotherapy, polytherapy, or total seizure number. Generalised tonic-clonic seizure frequency remained strongly associated with an increased risk for SUDEP. The number of generalised tonic-clonic seizures independently increased SUDEP risk. These results suggest that prevention of SUDEP must involve increased efforts to decrease generalised tonic-clonic seizure frequency in order to avert the occurrence of this devastating epilepsy outcome. In a recently published review of epidemiologic studies of premature mortality associated with epilepsy across all ages in high income countries by the ILAE Mortality Taskforce, all 9 population-based studies reported an increased risk of premature mortality among people with epilepsy compared to general populations. All these studies showed significant elevations of their SMRs ranging from 1.6 to 3.0. Among these, 3 studies involving children also reported considerably higher SMRs ranging from 6.4 to 7.5. Two clinic-based cohort studies yielded higher SMRs of 7.0 and 7.5 in children compared to 1.4 to 3.6 in adults or across all ages. (Thurman, et al. 2017)
Important co-morbidities	• Learning disabilities/cognitive impairments • Depression • Psychosis • Attention-deficithyperactivity disorder • Generalised anxiety disorders • Social phobia • Panic disorder • Sleep disturbances • Autism

AED=antiepileptic drug, CNS=central nervous system, ILAE = International League Against Epilepsy, PGTC=primary generalised tonic-clonic, SMR=Standardised Mortality Ratio, SUDEP=sudden unexpected death in epilepsy.

Part II Module SII - Nonclinical Part of the Safety Specification

Table 3 Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
• Toxicity o Single- and repeat-dose toxicity	In repeat-dose toxicology studies, administration of maximum tolerated doses to rats and cynomolgus monkeys resulted in pharmacologically-based CNS-related clinical signs and decreased terminal body weight. These are expected findings for an AMPA antagonist. There were no changes directly attributable to perampanel in clinical pathology or histopathology.	In clinical studies, a dose-related trend in the incidence of CNS-related AEs has been observed. Central nervous system-related AEs are not uncommon with antiepileptic agents.
• Reproductive/ developmental toxicity o Fertility	In a rat fertility study, prolonged and irregular estrous cycles were observed at high-dose (30 mg/kg) in females. However, these changes did not affect fertility or early embryonic development.	The dose at which these changes were observed was accompanied by expected CNS-related clinical signs, and thus the changes were likely to be secondary to CNS clinical signs and decreased body weight and food consumption. There is no evidence of effects on estradiol cycle or early menopause in any clinical studies. Therefore, the risk is unlikely to be relevant to human use.

Table 3 Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
• Reproductive/ developmental toxicity (continued)		
o Pregnancy/ nursing	In a perinatal/postnatal study in rats, abnormal delivery and nursing conditions were observed at 3 and 10 mg/kg, and the number of stillbirths was increased in offspring. In addition, the birth index and the viability index at 4 days after birth tended to be low at 3 and 10 mg/kg, and suppression of body weight gains and delayed morphologic differentiation (delayed opening of vaginal orifice or cleavage of balanopreputial skin fold) were noted at 10 mg/kg in offspring. However, no effects were observed in behavioural or reproductive function in the offspring. Perampanel is excreted in milk after oral administration to lactating female rats. The levels in milk were approximately 3.7-times higher than those in the plasma.	These changes in nursing mothers and offspring occurred at doses that caused decreased body weight and food consumption and CNS-related clinical signs in maternal animals, and are likely to be secondary to maternal toxicity. The relevance of these findings to humans is not known since there are no adequate studies in pregnant or nursing women. Perampanel should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. It is not known whether perampanel is excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from perampanel therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the mother.
o Fetal development	In the rabbit embryo fetal development studies, premature delivery was observed at high dose (10 mg/kg). No effects on fetuses were observed.	Decreased body weight and food consumption and CNS clinical signs were observed and the premature delivery was more likely to be secondary to these changes. However, the relevance of these findings for humans is not known, since there are no adequate and well-controlled studies in pregnant women. Perampanel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Table 3 Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
• Use in patients <12 years of age	In juvenile animal repeat-dose toxicity studies in rats and dogs, increased sensitivity to perampanel adverse reactions was observed as compared to adult animals at similar exposure levels. The adverse effects included CNS-related excessive pharmacological effects (decreased activity, abnormal gait, and lack of coordination, prostration) and associated reduction in growth progression (body weight and bone measurements [rats only]) and decreased food consumption (rat only). The effects on growth are believed to be secondary to the pharmacologically-based CNS clinical signs. The effect upon growth progression showed signs of recovery following cessation of the treatment. There were no effects on measures of learning or behaviour and the animals demonstrated normal reproductive function. In juvenile dogs, no adverse effects on body weight, food consumption, growth measurements, or on CNS development (behavioural and neurological evaluation) were observed.	Results from 2 open-label studies (Study E2007-G000-232 and Study 2001-G000-311) showed the use of perampanel to be generally safe and well-tolerated when used as adjunctive therapy in children 2 to <12 years of age. The majority of SAEs and other significant events were transient and manageable. No notable effects of perampanel on growth were reported. No new safety signals were identified in paediatric subjects 2 to <12 years of age.

Table 3 Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
• Phototoxicity	Positive results for perampanel were obtained in the in vitro 3T3 NRU phototoxicity test and the in vitro chromosomal aberration test in Chinese Hamster V79 cells with UV irradiation.	The relevance of positive findings in the in vitro phototoxicity tests for humans is not known. However, perampanel did not show any photoirritation effects in the in vivo studies (the photoirritation and photoallergy studies in albino hairless guinea pigs, photocarcinogenic responses in a 13-week oral albino hairless mice study, and photocarcinogenic biomarker investigation in skin tissues from a 39-week chronic study in monkeys). In addition, perampanel was negative in the in vitro photo-Ames assay. No signal of photosensitivity has been observed in humans. The data include a photosensitivity study in healthy volunteers and a photosensitivity questionnaire administered in the Phase 3 studies. Taken together, the totality of evidence suggests that the risk for photoirritation, photoallergy, and photocarcinogenicity in humans is low.
• Nephrotoxicity	No nephrotoxicity was observed in nonclinical toxicology studies.	To date, no evidence of nephrotoxicity related to the use of perampanel has been observed in healthy subjects or patient populations.
• Hepatotoxicity: Binding of perampanel in liver	After oral administration of [^{14}C]perampanel to rats and monkeys, nonextractable radioactivity was seen in liver, which may suggest covalent or tight binding to endogenous macromolecules of liver. However, no hepatic toxicity was observed in the repeat-dose toxicity studies in rats and monkeys. Therefore, this type of binding may be considered biologically insignificant.	The relevance of this finding for humans is not known. In nonclinical studies, no hepatic toxicity was observed in the chronic repeat-dose toxicology studies. In clinical studies, no significant changes in liver enzymes were observed. Therefore, the risk for human use is likely to be insignificant.

Table 3 Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
• Genotoxicity/ Carcinogenicity	Perampanel showed no mutagenic or clastogenic potential in any test system. Perampanel administered orally to mice (1, 3, 10, or 30 mg/kg/day) and rats (10, 30, or 100 mg/kg/day in males; 3, 10, or 30 mg/kg/day in females) for up to 104 weeks showed no evidence of drug-related tumours in either species.	To date, no evidence of genotoxicity or carcinogenicity related to the use of perampanel has been observed in healthy subject or patient populations.
• Safety pharmacology o Cardiovascular system (including potential effect on the QT interval)	There were no significant effects on the cardiovascular system (heart rate, mean blood pressure, and ECG) in dogs. The lack of effect on ECG parameters in the in vivo studies in dogs and weak inhibitory effects of perampanel in the hERG assay (IC_{50}: 15.8 µmol/L, 5.5 µg/mL) suggest that perampanel has a relatively low potential to cause QT prolongation.	Definitive QTc Study E2007-A001-013, including PK/PD analysis, has not shown a signal for QTc prolongation with perampanel. Pooled data from ECGs in the Phase 3 program, also including PK/PD analysis, have not shown a signal for QTc prolongation with perampanel. Review of the cardiac AEs has reached similar conclusions. Taken together, QTc prolongation is not considered to be a risk for human use.

Table 3 Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
○ Binding of perampanel to elastin and melanin	After oral administration in pigmented rats, [^{14}C]perampanel was bound to elastin of aorta and melanin of the ocular tissues. The terminal half-lives for the radioactivity in aorta and eyeball were 110 and 45 weeks, respectively. However, there were no drug-related histopathological lesions at any dose in the oral repeat-dose toxicology studies in mice, rats, dogs, or monkeys. As no evidence was reported for pathological changes in the aorta and eyes in chronic, repeat-dose toxicology studies in rats and monkeys, accumulation of perampanel-derived material could be considered an insignificant characteristic of perampanel. Slow elimination of radioactivity in the aorta might induce cardiovascular changes; however, perampanel did not have any serious adverse cardiovascular finding.	The relevance of these findings for humans is not known. There are no studies to address the effects of perampanel on elastin and melanin. Taken together and as there was no evidence of pathology reported in nonclinical studies, this is not considered to be a risk for human use.

Table 3 Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
• Mechanisms for drug interactions	The following in vitro metabolism studies were conducted using human hepatocytes: • Potential contribution of non-CYP metabolism study • Potential contribution of CYP isoforms in vitro study Potential contribution of non-CYP mediated metabolism was conducted using human hepatocytes and CYP inhibitor, ABT. Furthermore, the effect of CYP isoform specific inhibitors was investigated to estimate the contribution of each CYP isoform on perampanel metabolism in human liver microsomes. The results from both in vitro studies strongly suggest that potential contribution mediated by non-CYP and CYP isoforms other than CYP3A was of little importance on the overall metabolism of perampanel. Results from the mass balance study complement and confirm the findings of the in vitro studies. Based on results of the mass balance study, M15, one of the metabolites formed via a reactive intermediate, accounted for only 1.5% of dose in the excreta. Additionally, M15 was not detected in plasma in any subject. These findings indicate that M15 is a very minor metabolite.	In vitro studies support a conclusion that there is no or low risk of drug-drug interactions mediated other than CYP3A. It is concluded that the impact on exposure to the metabolites formed via reactive intermediates of inhibition of CYP1A2 and CYP3A, regardless of what assumptions are made for the metabolic route of formation of these metabolites, are minimal and no further clinical drug-drug interaction studies are needed.

Table 3 Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
• Other toxicity-related information or data	Not applicable	Not applicable.
Drug abuse, misuse, dependency, and withdrawal	In the rat physical dependency study, withdrawal signs were observed in perampanel-treated groups during the withdrawal period, suggesting potential for producing physical dependence in rats. In the monkey psychological dependency study to evaluate reinforcing effects, perampanel possessed reinforcing effects in monkeys; however, the potential was relatively weak.	The results from animal studies suggest that perampanel may have potential to cause physical dependence and reinforcing effects. However, this potential was relatively weak when compared to positive controls in animal studies. Two clinical studies were conducted in recreational polydrug users and the results suggested that the abuse potential of perampanel is no greater than benzodiazepines, and probably less, although it has some level of abuse potential. Drug discrimination procedures have often been used to help characterise the CNS effects and predict the abuse potential of new drugs, and there is a strong positive relationship between discriminative stimulus effects of drugs in non-humans and the subjective effects of the same drugs in humans. However, generalisation with an active substance known to cause dependence in itself is not necessarily indicative of dependence potential. Rather, the results should indicate whether or not perampanel is likely to have subjective effects that are qualitatively similar to prototypic drugs of abuse. A drug discrimination study in rats (Study 463-049) has examined the potential similarity of the interceptive or subjective effects of perampanel to those engendered by either ketamine or diazepam. The abuse potential of perampanel was lower than either ketamine or diazepam. Taken together, the risk of abuse potential is low and has been fully evaluated. Two studies in known drug abusers (Study E2007-A001-023 and Study E2007-A001-024) and an Abuse Potential Evaluation Report (Module 5.3.5.3) are included in the dossier.

ABT=aminobenzotriazole, AE=adverse event, AMPA=α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate, CNS=central nervous system, CYP=Cytochrome, ECG=electrocardiogram, hERG=human ether-a-go-go-related gene, IC_{50}=half maximal inhibitory concentration, NRU=neutral red uptake, PK/PD=pharmacokinetics/pharmacodynamics, QT interval=a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle, QTc=corrected QT interval, SAE=serious adverse event.

Part II Module SIII - Clinical Trial Exposure

Table 4 Total Subject Exposure to Perampanel in Clinical Trials by Indication

Indication	Subjects With Perampanel Exposure (N)[a]
Phase 1 Studies	1227
Healthy volunteers	1215
Hepatically impaired	12
Epilepsy	3034
Parkinson's disease	2137
Neuropathic pain	461
Migraine headaches	101
Multiple sclerosis	18
Total	6978[b]

a: Includes patients and healthy volunteers as of 22 Jul 2019 based on actual exposure data from completed clinical trials and enrollment/randomization schemes for ongoing studies.

b: Figures include patients who received both placebo and perampanel in the open-label extension parts of studies, and does not include exposure in the non-interventional study E2007-G000-402.

Table 5 Total Subject Exposure to Perampanel in Clinical Trials by Age Group and Gender

	Number of Subjects[a,b]		
Age Group	**Male**	**Female**	**Total**
<12 years	129	111	240
≥12 to <18 years	210	176	386
≥18 to <65 years	2736	2166	4902
≥65 years	731	544	1275
Total	3806	2997	6803[b]

a: Includes patients and healthy volunteers as of 22 Jul 2019 based on actual exposure data from completed clinical studies and enrollment/randomisation schemes for ongoing studies. Exposure data in <18 years of age were from patients only.

b: Does not include subjects from ongoing studies E2007-J081-240, E2007-G000-338, E2007-J000-342, and E2007-G000-401, since the demographic split or ethnicity data are currently not available.

Table 6 Total Subject Exposure to Perampanel in Clinical Trials by Ethnic Origin

Ethnic Origin	Number of Subjects[a,b]
Caucasian	4858
Black	239
Asian	1535
Other	151
Unclassified in database	11
Not yet known	105
Total	6899

a: Includes patients and healthy volunteers as of 22 Jul 2019 based on actual exposure data from completed clinical studies and enrollment/randomisation schemes for ongoing studies.

b: Does not include new subjects enrolled during this reporting period from ongoing studies E2007-J081-240, E2007-G000-338, and E2007-G000-410, since ethnicity data are not available.

Part II Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Table 7 Important Exclusion Criteria in Pivotal Studies Across the Development Programme

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Hypersensitivity to perampanel	Hypersensitivity reactions have been associated with morbidity and mortality in all populations.	No	Hypersensitivity reactions of SCARs including DRESS are addressed in Section 4.4 of the SmPC, Special warnings and precautions for use.
Who were pregnant and/or lactating	There are no adequate and well-controlled studies in pregnant women. Perampanel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known whether perampanel is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when perampanel is administered to a nursing woman.	Yes	

DRESS=drug reaction with eosinophilia and systemic symptoms, SCARs=severe cutaneous adverse reactions, SmPC=Summary of Product Characteristics.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme with perampanel did not have sufficient power to detect rare adverse reactions.

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table 8 Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure

Pregnant women	Not included in the clinical development programme.
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical studies	Not included in the clinical development programme.
Population with relevant different ethnic origin	Details of the number of patients exposed to perampanel in completed clinical studies by race are provided in Module SIII.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development programme.
Other • Paediatric patients	Details of the number of patients exposed to perampanel in completed clinical studies by age are provided in Module SIII.
• Elderly patients	Details of the number of patients ≥65 years of age exposed to perampanel in clinical studies are provided in Module SIII.

Part II Module SV - Postauthorisation Experience

SV.1 Postauthorisation Exposure

SV.1.1 Method Used to Calculate Exposure

Exposure has been calculated based on the World Health Organization defined daily dose of 8 mg.

SV.1.2 Exposure

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

Table 9 Patient Days of Exposure for the European Union and European Economic Area by Regions, North America and Rest of World by Country From International Birth Date Through June 2018

Country	Patient-Days of Exposure[a]
Australia	727,830
Austria	991,608
Belgium	388,579
Canada	1,160,619
Czech Republic	402,420
Denmark	443,153
Finland	222,759
France	4,954,341
Germany	1,607,267
Greece	629,032
Hong Kong	84,994
Iceland	negligible
India	719,621
Ireland	283,348
Israel	285,549
Italy	1,814,749
Japan	4,037,593
Jordan	9,721
Korea	2,761,070
Kuwait	13,498
Lebanon	50,986
Malaysia	84,418
Malta	negligible
Netherlands	451,456

Table 9 Patient Days of Exposure for the European Union and European Economic Area by Regions, North America and Rest of World by Country From International Birth Date Through June 2018

Country	Patient-Days of Exposure[a]
Norway	320,849
Portugal	847,632
Philippines	231,520
Russia	223,501
Saudi Arabia	47,028
Singapore	62,771
Slovakia	163,191
South Africa	12,199
Spain	7,901,107
Sweden	541,597
Switzerland (including Liechtenstein)	512,437
Taiwan	807,354
Thailand	232,986
United Arab Emirates	9758
United Kingdom	4,169,998
United States	6,736,220

Note: Sales data sets in the European Union territories are accumulated on a monthly basis and all data sets start at the beginning of a month and finish at the end of a month. 01 Jul 2012 to 30 Jun 2018 is selected as the latest complete data set available and nearest to the end date requested of 22 Jul 2018.

a: Total mgs divided by 8 mg.

Part II Module SVI - Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

Perampanel acts via selective noncompetitive inhibition of AMPA-type glutamate receptor activity. Currently known drugs of abuse do not act via the AMPA receptors. Preclinical studies assessing the effects of other AMPA receptor antagonists have not shown these drugs to have significant abuse potential or to potentiate the effects of other drugs of abuse. Rather, some studies have shown these drugs to reduce the effects of drugs of abuse including cocaine and alcohol. The effect of AMPA antagonists does not generalise to N-Methyl-D-aspartic acid (NMDA) antagonists, and vice versa, and thus one would not predict AMPA antagonists to have the same pharmacologic effect as an NMDA antagonist (eg, phencyclidine, ketamine).

Perampanel showed no binding to abuse-related molecular targets including opioid receptors, serotonin (5-HT) and dopamine transporters and receptors, NMDA, gamma-aminobutyric acid, nicotinic acetylcholine, or cannabinoid receptors.

In a Phase 1 study to assess the safety and tolerability of single perampanel doses up to 36 mg in recreational polydrug abusers, there were elevations in Drug Liking and Good Drug Effects. The 28 mg dose was associated with the highest peak Drug Liking and Good Drug Effects, and these subjective effects did not appear to decline extensively over time. Both perampanel 24 mg and perampanel 28 mg had greater positive effects and relatively fewer negative effects. Bad drug effects also tended to increase with higher doses of drug (32 mg and 36 mg) suggesting that the potential abuse of perampanel may be dose limited. An important caveat is that this study was not designed with the intent of meeting criteria for a well-controlled human abuse liability study. Rather, it was designed primarily as a safety and tolerability study, which included some measures of abuse liability.

A human abuse potential study, which examined the effects of doses up to 36 mg, found dose-related elevations in several measures of Drug Liking relative to placebo indicating that perampanel does have some level of abuse potential. However, this abuse potential appears to be lower than ketamine. Specifically, perampanel produced elevations in scores indicative of positive subjective effects that were lower than those produced by ketamine, had a slower onset of effect, and produced negative effects that were persistent, in some cases as long as 48 hours after administration. Perampanel did produce positive effects that were comparable to alprazolam, both in magnitude of effect, onset of action, and duration of effect. Again however, perampanel produced negative effects that were higher than alprazolam, and which lasted longer. Further, on the drug identification questionnaire, perampanel was most often identified as a benzodiazepine. This would suggest that the abuse potential of perampanel is no greater than benzodiazepines, and probably less based on the profile of negative effects.

Adverse event data from clinical studies were examined to identify treatment emergent adverse events (TEAEs) that may be suggestive of abuse potential. With the exception of dizziness and sedative effects, the rates of these events was very low across all of the

Phase 1, 2, and 3 studies in which doses up to 12 mg were administered to subjects who were not recreational sedative abusers. There were few reports, but a rate higher than placebo, of TEAEs such as "euphoric mood" and "feeling drunk" that would be directly indicative of abuse potential, and very few reports of hallucination. Further, the majority of these reports did not occur until after many days, weeks, months, or even years of taking the drug on a daily basis, which would not be a pattern seen with any prototypic drug of abuse. This indicates that there is little risk of abuse among the patient population, or among others who might be exposed to the drug.

Overall, the pharmacological activity profile of perampanel as observed in nonclinical pharmacological studies and PD evaluations in humans does not point to a specific concern regarding abuse or dependence liability. Specifically, the long half-life (25 to 105 hours) of the drug in humans would be predicted to reduce withdrawal symptoms and repeated self-administration of the drug.

Part II Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Not applicable. This is not the initial RMP for the product.

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable. This is not the initial RMP for the product.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable. This is not the initial RMP for the product.

SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

Table 10 New or Reclassification of Safety Concerns in the RMP

Safety Concern	Action Taken	Justification Reasons for the reclassification/removal/addition to the list of safety concerns:
New Safety Concerns		
Important Identified Risks		
Not applicable		
Important Potential Risks		
Hepatic disorders (excluding hepatic disorders induced by SCARs)	This is a new important potential risk.	The risk of hepatic disorders has been added as an important potential risk as requested by Pharmcovigilance Risk Assessment Committee (PRAC) in the review of PSUR #12 (data lock point of 22 Jul 2019) considering that a causal relationship between perampanel and hepatotoxicity cannot be excluded and needs to be further characterised.
Missing Information		
Not applicable		
Removal of Safety Concerns From RMP		
Important Identified Risks		
Dizziness	Dizziness previously classified as an important identified risk is removed from the list of safety concerns.	The MAH considers that this safety concern should be removed from the list of safety concerns since this risk is aqequately reflected in the product information and long-term monitoring has not required any additional risk minimisation activities.
Somnolence	Somnolence previously classified as an important identified risk is removed from the list of safety concerns.	The MAH considers that this safety concern should be removed from the list of safety concerns since this risk is aqequately reflected in the product information and long-term monitoring has not required any additional risk minimisation activities.
Balance disorder, ataxia, and falls	Balance disorder, ataxia, and falls (particularly in the elderly)	The MAH considers that this safety concern should be removed from the list of safety

Table 10 New or Reclassification of Safety Concerns in the RMP

Safety Concern	Action Taken	Justification Reasons for the reclassification/removal/addition to the list of safety concerns:
(particularly in the elderly)	previously classified as an important identified risk is removed from the list of safety concerns.	concerns since this risk is aqequately reflected in the product information and long-term monitoring has not required any additional risk minimisation activities.
Weight gain	Weight gain previously classified as an important identified risk is removed from the list of safety concerns.	Weight gain is not considered to have an impact on the benefit-risk balance of perampanel, eg, no warnings or precautions for use have been included in the product information. Additionally, long-term monitoring has not required any additional risk minimisation activities.
Blurred vision	Blurred vision previously classified as an important identified risk is removed from the list of safety concerns.	Blurred vision is not considered to have an impact on the benefit-risk balance of perampanel, eg, no warnings or precautions for use have been included in the product information. Additionally, long-term monitoring has not required any additional risk minimisation activities.
Important Potential Risks		
Drug abuse, misuse, dependency, and withdrawal	Drug abuse, misuse, dependency, and withdrawal previously classified as an important potential risk is removed from the list of safety concerns.	The MAH considers that this safety concern should be removed from the list of safety concerns since as noted above In Part II, Module SVI, the pharmacological activity profile of perampanel as observed in nonclinical pharmacological studies and PD evaluations in humans does not point to a specific concern regarding abuse or dependence liability. In addition, the long half-life (25 to 105 hours) of the drug in humans would be predicted to reduce withdrawal symptoms and repeated self-administration of the drug.
Off label usage	Off label usage previously classified as an important potential risk is removed from the list of safety concerns.	Since the therapeutic indications are described thoroughly in the product information and there is no additional risk minimisation activities, the MAH considers that this safety concern should be removed from the list of safety concerns.
Medication errors (especially with oral suspension formulation)	Medication errors, especially those associated with the oral suspension formula previously classified as an important potential risk is removed from the list of safety concerns.	Since the posology and method of administration is described thoroughly in the product information for tablets and oral suspension and there is no additional risk minimisation activities, the MAH considers that this safety concern should be removed from the list of safety concerns.

Table 10 New or Reclassification of Safety Concerns in the RMP

Safety Concern	Action Taken	Justification Reasons for the reclassification/removal/addition to the list of safety concerns:
Skin photosensitivity	Skin sensitivity previously classified as an important potential risk is removed from the list of safety concerns.	There is no evidence of skin photosensitivity with perampanel and there are no warnings or precautions for use included in the product information. Additionally, long-term monitoring has not identified this as a risk.
Missing Information		
Use in patients <12 years of age	Use in patients <12 years of age classified as missing information is removed from the list of safety concerns	Paediatric studies have been conducted and have not demonstrated additional risks justifying the proposal to remove from the list of safety concerns of missing information.
Long-term safety in adolescents and adults	Long-term safety in adolescents and adults classified as missing information is removed from the list of safety concerns	Additional studies have been conducted and have not demonstrated additional risks associated with long-term use.
Long-term effects of perampanel binding to elastin, melanin and hepatic cells	Long-term effects of perampanel binding to elastin, melanin and hepatic cells classified as missing information is removed from the list of safety concerns	This concern is not considered to have an impact on the benefit-risk balance of perampanel, eg, no warnings or precautions for use have been included in the product information. Long-term monitoring has not required any additional risk minimisation activities.

Table 10 New or Reclassification of Safety Concerns in the RMP

Safety Concern	Action Taken	Justification Reasons for the reclassification/removal/addition to the list of safety concerns:
Idiosyncratic reactions related to reactive metabolites	Idiosyncratic reactions related to reactive metabolites classified as missing information is removed from the list of safety concerns	This concern is not considered to have an impact on the benefit-risk balance of perampanel, eg, no warnings or precautions for use have been included in the product information. Additionally, long-term monitoring has not required any additional risk minimisation activities.
Use in patients with cardiovascular disease, hypertension, congestive heart failure, history of myocardial infarction or any evidence of risk factors for QT prolongation	Use in patients with cardiovascular disease, hypertension, congestive heart failure, history of myocardial infarction or any evidence of risk factors for QT prolongation classified as missing information is removed from the list of safety concerns	This concern is not considered to have an impact on the benefit-risk balance of perampanel, eg, no warnings or precautions for use have been included in the product information. Additionally, long-term monitoring has not required any additional risk minimisation activities.
Use in patients with a history of psychotic disorder or suicidal behaviour in the previous 2 years	Use in patients with a history of psychotic disorder or suicidal behaviour in the previous 2 years classified as missing information is removed from the list of safety concerns	This concern is not considered to have an impact on the benefit-risk balance of perampanel, eg, no warnings or precautions for use have been included in the product information. Additionally, long-term monitoring has not required any additional risk minimisation activities.
Use in patients with a history of drug or alcohol dependency	Use in patients with a history of drug or alcohol dependency classified as missing information is removed from the list of safety concerns	This concern is not considered to have an impact on the benefit-risk balance of perampanel, eg, no warnings or precautions for use have been included in the product information. Additionally, long-term monitoring has not required any additional risk minimisation activities.
Use in patients who are taking vigabatrin	Use in patients who are taking vigabatrin classified as missing information is removed from the list of safety concerns	This concern is not considered to have an impact on the benefit-risk balance of perampanel, eg, no warnings or precautions for use have been included in the product information. Additionally, long-term monitoring has not required any additional risk minimisation activities.

Table 10 New or Reclassification of Safety Concerns in the RMP

Safety Concern	Action Taken	Justification Reasons for the reclassification/removal/addition to the list of safety concerns:
Use in patients with hepatic insufficiency whether related to concomitant medications or underlying liver disease	Use in patients with hepatic insufficiency whether related to concomitant medications or underlying liver disease classified as missing information is removed from the list of safety concerns	This concern is not considered to have an impact on the benefit-risk balance of perampanel, eg, no warnings or precautions for use have been included in the product information. Additionally, long-term monitoring has not required any additional risk minimisation activities.
Use in patients with clinically significant renal or respiratory disease	Use in patients with clinically significant renal or respiratory disease classified as missing information is removed from the list of safety concerns	This concern is not considered to have an impact on the benefit-risk balance of perampanel, eg, no warnings or precautions for use have been included in the product information. Additionally, long-term monitoring has not required any additional risk minimisation activities.
Use in the elderly with epilepsy, with particular monitoring of dizziness, balance disorders and falls	Use in the elderly with epilepsy, with particular monitoring of dizziness, balance disorders and falls classified as missing information is removed from the list of safety concerns	This concern is not considered to have an impact on the benefit-risk balance of perampanel, eg, no warnings or precautions for use have been included in the product information. Additionally, long-term monitoring has not required any additional risk minimisation activities.

MAH = marketing authorisation holder, SCARs = severe cutaneous adverse reactions, SmPC=Summary of Product Characteristics.

SVII.3 Details of Important Identified Risks, Important Potential Risks and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Table 11 Important Identified Risk: Aggression

Potential mechanisms	Unknown.
Evidence source(s) and strength of evidence	Perampanel controlled clinical study data.
Characterisation of the risk (as applicable)	
Frequency	**Adjunctive therapy Phase 3 POS:** Aggression: 1.6% Irritability: 7.0% Anger: 1.2% Belligerence: 0.1% **Adjunctive therapy Phase 3 PGTC:** Aggression: 1.2%

Table 11 Important Identified Risk: Aggression

	Irritability: 11.1% **<u>Paediatric Study E2007-G000-311</u>** **Adjunctive therapy POS (N=149):** Aggression: 10.1% Irritability: 12.1% Anger: 1.3% **Adjunctive therapy PGTC (N=31):** Aggression: 3.2% Irritability: 16.1%
Severity	**Adjunctive therapy Phase 3 POS:** Aggression (% of subjects): mild (0.5%), moderate (0.9%) and severe (0.3%); irritability (% of subjects): mild (4.1%), moderate (2.5%) and severe (0.4%); anger (% of subjects): mild (0.7%), moderate (0.3%) and severe (0.2%). The event of belligerence was severe (0.1%). Events leading to study or study drug discontinuation (% of subjects): aggression (0.5%), irritability (0.4%), anger (0.4%), and belligerence (0.1%) **Adjunctive therapy Phase 3 PGTC:** Aggression (% of subjects): mild (1.2%); irritability (% of subjects): mild (7.4%) and moderate (3.7%). Events leading to study or study drug discontinuation (% of subjects): aggression (1.2%) and irritability (1.2%). **<u>Paediatric Study E2007-G000-311:</u>** **Adjunctive therapy POS (N=149):** Aggression (% of subjects): mild (3.4%), moderate (6.0%) and severe (0.7%); irritability (% of subjects): mild (10.1%), and moderate (2.0%). Two subjects experienced anger which was of moderate severity (1.3% subjects). Events leading to study or study drug discontinuation (% of subjects): aggression (2.0%), irritability (1.3%), and anger (0.7%). **Adjunctive therapy PGTC (N=31):** The aggression in 1 subject (3.2%) was moderate severity. All events (16.1% of subjects) of irritability were mild. Irritability led to study or study drug discontinuation for 1 subject (3.2%).
Reversibility	Events of aggression can potentially be reversed upon discontinuation of treatment.
Long-term outcomes	Aggression may affect interpersonal relationships.
Impact on quality of life	There is a potential risk of behavioural abnormalities affecting interpersonal relationships.
Risk groups and risk factors	Risk factors for a psychiatric disorder in patients with epilepsy are mental retardation, temporal lobe epilepsy (as opposed to other subtypes), and a high seizure frequency (Matsuura, et al. 2003). In patients with epilepsy treated with topiramate, family psychiatric history and family history of epilepsy, personal history of febrile convulsions, psychiatric

Table 11 Important Identified Risk: Aggression

	history, and presence of tonic-atonic seizures were found to be significant risk factors for developing psychiatric adverse events (Mula, et al. 2003).
Preventability	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.
Impact on the risk-benefit balance of the product	Routine risk minimisation measures have been implemented.
Public health impact	None identified.

PGTC=primary generalised tonic-clonic, POS=partial-onset seizures; SmPC=Summary of Product Characteristics.

Table 12 Important Identified Risk: Interaction With Levonorgestrel-Containing Contraceptives, and Unintended Pregnancy Exposures

Potential mechanisms	The combined effect of perampanel on levonorgestrel suggests that 12 mg QD of perampanel induced metabolism of levonorgestrel, but the induction did not appear to be CYP3A4-dependent.
Evidence source(s) and strength of evidence	Perampanel Study E2007-E044-029: 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.
Characterisation of the risk (as applicable)	
Frequency	In perampanel studies, no unintended pregnancy exposures due to interaction with levonorgestrel-containing contraceptives were reported.
Severity	Not applicable.
Reversibility	Not applicable.
Long-term outcomes	Not applicable.
Impact on quality of life	Not applicable.
Risk groups and risk factors	Women taking perampanel 12 mg and levonorgestrel-containing contraceptives.
Preventability	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.
Impact on the risk-benefit balance of the product	Routine risk minimisation measures have been implemented.
Public health impact	None identified.

QD=once daily

Table 13 Important Identified Risk: Suicidality

Potential mechanisms	Unknown
Evidence source(s) and strength of evidence	Perampanel controlled clinical study data
Characterisation of the risk (as applicable)	
Frequency	**Adjunctive therapy Phase 3 POS:** • Suicidal ideation: 0.2% • Multiple drug overdose intentional: 0.1% In all studies in subjects (total number: 1639) with refractory partial seizures, the event of suicide attempt was reported for 0.2% of subjects. **Adjunctive therapy Phase 3 PGTC:** • Suicidal ideation: 1.2% • Suicide attempt: 1.2% **Paediatric Study E2007-G000-311** **Adjunctive therapy POS (N=149):** There were no events of suicidal ideation. **Adjunctive therapy PGTC (N=31):** Suicidal ideation: 3.2%
Severity	**Adjunctive therapy Phase 3 POS:** Suicidal ideation (% of subjects): moderate (0.1%) and severe (0.1%); multiple drug intentional overdose (% of subjects): severe (0.1%). Events leading to study or study drug discontinuation (% of subjects): suicidal ideation (0.2%) and multiple drug intentional overdose (0.1%). In all studies in subjects with refractory partial seizures, the 3 subjects with SAEs of suicide attempt were reported as severe and 1 led to study or study drug discontinuation. **Adjunctive therapy Phase 3 PGTC:** Suicidal ideation and suicide attempt (% of subjects): severe (1.2%). Study drug was discontinued for both subjects (1.2%). **Paediatric Study E2007-G000-311:** **Adjunctive therapy POS (N=149):** There were no events of suicidal ideation. **Adjunctive therapy PGTC (N=31):** The suicidal ideation reported for 1 subjects (3.2%) was mild in severity and did not result in study discontinuation.
Reversibility	Thoughts of suicidality can potentially be reversed upon discontinuation of treatment.

Table 13 Important Identified Risk: Suicidality

Long-term outcomes	There have been serious reports of suicidality.
Impact on quality of life	Not applicable.
Risk groups and risk factors	High suicide rate among epileptic patients has a greater association with psychotic behaviours and psychic auras than with major depression or the psychosocial burden of being epileptic (Mendez and Doss, 1992). In a case-control study of persons diagnosed with epilepsy, there was a 9-fold increase in risk of suicide with mental illness and a 10-fold increase in relative risk (RR) with the use of antipsychotic drugs. The estimated RR of suicide was 16.0 (95% CI, 4.4-58.3) for onset of epilepsy at younger than 18 years, compared with onset after 29 years. The risk of suicide seemed to increase with high seizure frequency and AED polytherapy (Nilsson, et al. 2002). The highest risk of suicide exists in patients with epilepsy and comorbid psychiatric disease, even after adjusting for socioeconomic factors (13.7, 11.8-16.0; $P<0.0001$). In individuals with epilepsy, the highest risk of suicide was found during the first half year after diagnosis was made (5.35, 3.43-8.33; $P<0.0001$), and was especially high in those with a history of comorbid psychiatric disease (29.2, 16.4 51.9; $P<0.0001$) (Christensen, et al. 2007).
Preventability	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.
Impact on the risk-benefit balance of the product	Routine risk minimisation measures have been implemented.
Public health impact	Although the potential public health impact of suicidality in general is always significant, the small number of suicides in patients treated with AEDs does not allow any conclusions about their effect on suicide.

AED=anti-epilepsy drug, PGTC=primary generalised tonic-clonic, POS=partial-onset seizures, RR=relative risk, SAE=serious adverse event.

Table 14 Important Potential Risk: Hepatic Disorders (Excluding Hepatic Disorders Induced by Severe Cutaneous Adverse Reactions)

Potential mechanisms	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.
Evidence source(s) and strength of evidence	Postmarketing cases, and a trend of higher rate of non-serious hepatic events on perampanel compared to placebo in clinical trials.
Characterisation of the risk (as applicable)	
Frequency	No SAEs associated with this risk reported in clinical studies with epilepsy. Non-serious events were reported in 138 (2.49%) subjects on perampanel compared to 25 (1.32%) of subjects on placebo in clinical trials.
Severity	Not applicable.
Reversibility	Events can potentially be reversed upon discontinuation of treatment.
Long-term outcomes	Not applicable.
Impact on quality of life	Not applicable.
Risk groups and risk factors	None identified.
Preventability	No factors known.
Impact on the risk-benefit balance of the product	Routine risk minimisation measures have been implemented.
Public health impact	None identified

SAEs = serious adverse events

SVII.3.2 Presentation of the Missing Information

Table 15 Missing Information: Impact on Cognition and Growth in the Paediatric Population

Evidence source	Clinical studies in paediatric population
Population in need of further characterisation	There are limited amounts of long-term data in the paediatric population.

Table 16 Missing Information: Use in Human Pregnancy and Lactation

Evidence source	There has been limited exposure to perampanel in patients who have become pregnant.
Population in need of further characterisation	There are limited amounts of data from the use of perampanel in pregnant women. Studies in animals did not indicate any teratogenic effects in rats or rabbits, but embryotoxicity was observed in rats at maternally toxic doses. Section 4.6 of the SmPC notes that perampanel is not recommended in women of childbearing potential not using contraception unless clearly necessary. Eisai contributes to the UK Epilepsy and Pregnancy Registry as well as the European and International Registry of Anti-Epileptic Drugs in Pregnancy (EURAP). The primary objective of EURAP is to evaluate and determine the comparative risk of major fetal malformations following intake of AEDs (old and new) and their combinations during pregnancy.

AED=antiepileptic drug, EURAP=European and International Registry of Anti-Epileptic Drugs in Pregnancy, SmPC=Summary of Product Characteristics.

Part II Module SVIII - Summary of the Safety Concerns

Table 17 Summary of Safety Concerns

Important identified risks	Aggression Interaction with levonorgestrel-containing contraceptives, and unintended pregnancy exposures Suicidality
Important potential risks	Hepatic disorders (excluding hepatic disorders induced by SCARs)
Missing information	Impact on cognition and growth in the paediatric population Use in human pregnancy and lactation

SCARs = severe cutaneous adverse reactions

PART III PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Table 18 Specific Adverse Reaction Follow-Up Questionnaires for Aggression and Suicidality and Exposure During Pregnancy

Follow-Up Questionnaire	Safety Concern(s)	Purpose
Questionnaire for reports of Aggression	Aggression	Follow-up questionnaire for serious reports of aggression to obtain complete information.
Questionnaire for reports of suicidal behaviour, ideation, attempt or self-injurious behaviour	Suicidality	Follow-up questionnaire for serious reports of suicidality to obtain complete information
Questionnaire for reports of exposure during pregnancy	Use in human pregnancy and lactation	Follow-up questionnaire to obtain complete information on pregnancy outcomes

Table 19 Other Forms of Routine Pharmacovigilance Activities for Pregnancy

Description of Activity	Safety Concern(s)	Objectives	Milestones
• Contribution to EURAP registry • Contribution to the UK Epilepsy and Pregnancy Registry	Use in human pregnancy and lactation	To collect data on pregnancy exposure and outcomes with the use of Fycompa	Review pregnancy information provided by EURAP

EURAP=European and International Registry of Anti-Epileptic Drugs in Pregnancy.

III.2 Additional Pharmacovigilance Activities

Not applicable.

III.3 Summary Table of Additional Pharmacovigilance Activities

Not applicable.

PART IV PLANS FOR POSTAUTHORISATION EFFICACY STUDIES

No post-authorisation efficacy studies are planned.

PART V RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Table 20 Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Important Identified Risks	
Aggression	Routine risk communication: SmPC Section 4.4, where recommendations for perampanel dose reduction or discontinuation are provided. SmPC Section 4.8 PL Section 2, Section 4 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 Section 4.4 of the SmPC. Other routine risk minimisation measures beyond the Product Information: None.
Interaction With Levonorgestrel-Containing Contraceptives, and Unintended Pregnancy Exposures	Routine risk communication: SmPC Section 4.4, Section 4.5, Section 4.6 PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable Other routine risk minimisation measures beyond the Product Information: None.
Suicidality	Routine risk communication: SmPC Section 4.4, Section 4.8 PL Section 4 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 Section 4.4 of the SmPC. Other routine risk minimisation measures beyond the Product Information: None.

Table 20 Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Important Potential Risks	
Hepatic disorders (excluding hepatic disorders induced by SCARs)	Routine risk communication: SmPC Section 4.4 PL Section 2 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: SmPC Section 4.8 and 5.1 Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable Other routine risk minimisation measures beyond the Product Information: None.
Use in human pregnancy and lactation	Routine risk communication: SmPC Section 4.6 PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable Other routine risk minimisation measures beyond the Product Information: None.

PL=Package Leaflet, SCARs = severe cutaneous adverse reactions, SmPC=Summary of Product Characteristics.

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

Table 21 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Aggression	Routine risk minimisation measures: • SmPC Section 4.4, where recommendations for perampanel dose reduction or discontinuation are provided • SmPC Section 4.8 • PL Section 2 • PL Section 4	Routine PV activities including targeted follow-up
Interaction With Levonorgestrel-Containing Contraceptives, and Unintended Pregnancy Exposures	Routine risk minimisation measures: • SmPC Section 4.4 • SmPC Section 4.5 • SmPC Section 4.6 • PL Section 2	Routine PV activities
Suicidality	Routine risk minimisation measures: • SmPC Section 4.4, where advice for monitoring signs of suicidality is provided • SmPC Section 4.8 • PL Section 4	Routine PV activities including targeted follow-up
Important Potential Risks		
Hepatic Disorders (excluding hepatic disorders induced by SCARs)	Routine risk minimisation measures: • SmPC Section 4.4 • PL Section 2	Routine PV activities

Table 21 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Missing Information		
Impact on cognition and growth in the paediatric population	Routine risk minimisation measures: SmPC Section 4.8 and Section 5.1	Routine PV activities
Use in Human Pregnancy And Lactation	Routine risk minimisation measures: • SmPC Section 4.6 • PL Section 2	Routine PV activities including follow-up questionnaire to obtain complete information on pregancy outcomes

PL=Package Leaflet, PV=pharmacovigilance, SCARs = severe cutaneous adverse reactions, SmPC=Summary of Product Characteristics.

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan (RMP) for Fycompa.

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

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

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

I The Medicine and What it is Used for

Fycompa is authorised for the adjunctive treatment of partial onset (focal) seizures (POS) with or without secondarily generalised seizures in adults and children from 2 years of age with epilepsy and for the adjunctive treatment of primary generalised tonic-clonic (PGTC) seizures in adults and children from 2 years of age with idiopathic generalised epilepsy (see SmPC 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.

Further information about the evaluation of Fycompa's benefits can be found in Fycompa's European Public Assessments Report (EPAR), including in its plain-language summary, available on the EMA website, under the medicine's webpage: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/002434/WC500130840.pdf.

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 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 (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).

List of Important Risks and Missing Information

Important identified risks	• Aggression • Interaction with levonorgestrel-containing contraceptives, and unintended pregnancy exposures • Suicidality
Important potential risks	• Hepatic disorders (excluding hepatic disorders induced by SCARs)
Missing information	• Impact on cognition and growth in the paediatric population • Use in human pregnancy and lactation

II.B Summary of Important Risks

Important Identified Risks	
Aggression	
Evidence for linking the risk to the medicine	Perampanel controlled clinical study data.
Risk factors and risk groups	Risk factors for a psychiatric disorder in patients with epilepsy are mental retardation, temporal lobe epilepsy (as opposed to other subtypes), and a high seizure frequency (Matsuura, et al. 2003). In patients with epilepsy treated with topiramate, family psychiatric history and family history of epilepsy, personal history of febrile convulsions, psychiatric history, and presence of tonic-atonic seizures were found to be significant risk factors for developing psychiatric adverse events (Mula, et al. 2003).
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4, where recommendations for perampanel dose reduction or discontinuation are provided • SmPC Section 4.8 • PL Section 2 • PL Section 4
Interaction with Levonorgestrel-Containing Contraceptives, and Unintended Pregnancy Exposures	
Evidence for linking the risk to the medicine	Perampanel Study E2007-E044-029: 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.
Risk factors and risk groups	Women taking perampanel 12 mg and levonorgestrel-containing contraceptives.
Risk minimisation measures	Routine risk minimisation measures:

	• SmPC Section 4.4 • SmPC Section 4.5 • SmPC Section 4.6 • PL Section 2
Important Identified Risks (continued)	
Suicidality	
Evidence for linking the risk to the medicine	Perampanel controlled clinical study data
Risk factors and risk groups	High suicide rate among epileptic patients has a greater association with psychotic behaviours and psychic auras than with major depression or the psychosocial burden of being epileptic (Mendez, et al. 1992). In a case-control study of persons diagnosed with epilepsy, there was a 9-fold increase in risk of suicide with mental illness and a 10-fold increase in relative risk (RR) with the use of antipsychotic drugs. The estimated RR of suicide was 16.0 (95% CI, 4.4-58.3) for onset of epilepsy at younger than 18 years, compared with onset after 29 years. The risk of suicide seemed to increase with high seizure frequency and AED polytherapy (Nilsson, et al. 2002). The highest risk of suicide exists in patients with epilepsy and comorbid psychiatric disease, even after adjusting for socioeconomic factors (13.7, 11.8-16.0; $P<0.0001$). In individuals with epilepsy, the highest risk of suicide was found during the first half year after diagnosis was made (5.35, 3.43-8.33; $P<0.0001$), and was especially high in those with a history of comorbid psychiatric disease (29.2, 16.4 51.9; $P<0.0001$) (Christensen, et al. 2007).
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4, where advice for monitoring signs of suicidality is provided • SmPC Section 4.8 • PL Section 4
Important Potential Risks	
Hepatic Disorders (excluding hepatic disorders induced by SCARs)	
Evidence for linking the risk to the medicine	Post-marketing reports
Risk factors and risk groups	None identified
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4 • PL Section 2
Missing Information	
Impact on Cognition and Growth in the Paediatric Population	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.8 and Section 5.1

Use in Human Pregnancy and Lactation	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.6 • PL Section 2

II.C Postauthorisation Development Plan

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

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

II.C.2 Other Studies in Postauthorisation Development Plan

Not applicable.

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Follow-Up Form Title	Version Number	Date of Follow-Up Version
Aggression	Not applicable	29 Jan 2014
Suicidal behaviour, ideation, attempt or self-injurious behaviour	Not applicable	29 Jan 2014
Pregnancy Report Form and Spontaneous Pregnancy Outcome Report Form	Not applicable	March 2012 and January 2013

Aggression Follow-up Form

Questions for a report of Aggression, Violence, Physical Assault, and similar events:

1. It would be very helpful if you could describe the event in as much detail as possible, including whether the manifestation of the aggression was verbal or physical or both and whether the patient was under the influence of alcohol, narcotics, cannabis or illegal drugs at the time of the event.

2. Was the aggression observed immediately following a seizure? Yes/ No

3. Was the aggression observed with any other psychiatric symptoms such as psychotic symptoms of delusions or hallucinations? Yes/ No

    a. If Yes, please describe.

4. Any previous history of aggression, irritability, hostility, anger, violence, agitation or paranoia. Yes/No

    a. If Yes, please provide details.

5. Any past or current history of other psychiatric disorders (eg, depression, bipolar disorder, impulse control disorders, psychotic symptoms, etc). Yes/No

    a. If Yes, please provide details

6. Any past or current history of alcohol or drug abuse? Yes/No

    a. If Yes, please provide details

7. Any history of head injury? Yes/ No

    a. If Yes, please provide details of when it occurred etc.

Suicidal Behaviour, Ideation, Attempt or Self-Injurious Behaviour Follow-Up Form

Questions for a report of Suicidal behavior, suicidal ideation, suicide attempt or self-injurious behaviour:

1. It would be very helpful if you could describe the event in as much detail as possible.
2. Any previous history of this behavior? Yes/No
    a. If Yes, please provide details.
3. Any past or current history of other psychiatric disorders (eg, depression, bipolar disorder, impulse control disorders, psychotic symptoms, etc). Yes/No
    a. If Yes, please provide details
4. Any past or current history of alcohol or drug abuse? Yes/No
    a. If Yes, please provide details
5. Any recent changes or stresses in the patient's situation (ie, death of family member, loss of job, etc.)? Yes/No
    a. If Yes, please provide details
6. Any other significant health problems (ie, chronic pain, cancer, severe heart disease, etc.)? Yes/No
    a. If Yes, please provide details
7. Any family history of suicide, mental disorder or substance abuse? Yes/No
    a. If Yes, please provide details

Reporter:
Name _____
Address: _____
_____
City_____ State_____ Zipcode _____

DEMOGRAPHY AND MEDICAL HISTORY

Patient: Number/Initials	Race: _____ Age: _____ years Date of birth: / /		Weight : _____ Pounds Height: _____ Inches
_____/_____			

Known allergies: No ☐ Yes ☐ (specify) _____
Alcohol intake: No ☐ Yes ☐ (specify) _____
Other significant prior or co-existent medical conditions or history: No ☐ Yes ☐ (specify)
_____
_____
_____
Was the subject using contraception at the time of conception: No ☐ Yes ☐ (specify contraceptive measure)_____

PREGNANCY INFORMATION

	mm/dd/yy
Start date of last menstrual period	____/____/____
Date of positive pregnancy test	____/____/____
Date of last negative pregnancy test	____/____/____
Was pregnancy terminated?	No ☐ Yes ☐ If yes, date ____/____/_____
Date of expected delivery	____/____/_____
Number of previous pregnancies	_____
Number of live births	_____

Has patient experienced complications during this or previous pregnancies? No ☐ Yes ☐
If yes, specify_____
_____

CONCOMITANT DRUGS

Drug (generic name)	Total daily dose	Route	Dates of Administration From mm/dd/yy	To** mm/dd/yy	Indication

PATIENT STATUS
Complete Applicable Areas Only

At Onset of Pregnancy:

End of 1st Trimester:

End of 2nd Trimester:

Outcome:

Comments:

Physician's Signature: _____ Date: (mm/dd/yy) ____/____/_____

FOR COMPANY USE ONLY		
a. Date this report initially received by Eisai: (dd/Mmm/yyyy)	b. ARISg No:	c. Local No:

SPONTANEOUS PREGNANCY OUTCOME REPORT FORM

Version (January 2013)

Suspect Company Drug:	Reporter Name:	Occupation:
Indication for drug:	Telephone Number:	
Address:	Country:	

A. SUBJECT IDENTIFICATION

Subject: Initials ( )	Age: _____ years Date of birth: ____/____/____ (dd/Mmm/yyyy)

B. PREGNANCY OUTCOME INFORMATION

Outcome: Length of gestation _____ weeks

Voluntary Termination (Induced Abortion)* ☐ Spontaneous Abortion (Miscarriage)* ☐ Delivery ☐

Date of delivery(dd/Mmm/yyyy): ____/____/____

Method of delivery (select one) Vaginal ☐ Cesarean section ☐

Number of births as a result of this pregnancy _____ (include live and stillbirth)

C. CHILD INFORMATION

Baby #1 initials ____/____/____	Sex Male ☐ Female ☐	Height: _____ ☐ inches ☐ cm Weight : _____ ☐ lbs ☐ kgs _____ ☐ oz	Apgar score 1 minute _____ 5 minutes _____

Outcome of pregnancy: Normal ☐

Abnormal baby ☐ specify below

Congenital abnormality* ☐ specify below

Died during Perinatal Period* ☐ specify below

_____

_____

Baby #2 initials ____/____/____	Sex Male ☐ Female ☐	Height: _____ ☐inches ☐cm Weight : _____ ☐lbs ☐ kgs _____ ☐oz	Apgar score 1 minute _____ 5 minutes _____
Outcome of pregnancy: Normal ☐ Abnormal baby ☐ specify below Congenital abnormality* ☐ specify below Died during Perinatal Period* ☐ specify below _____ _____			
Reporter's Signature: _____ Date: (dd/Mmm/yyyy) ____/____/____			

* If additional pages are required to describe a pregnancy outcome, please append separately to this form.

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable.