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Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Fycompa

perampanel

Procedure no: EMEA/H/C/002434/P46/017

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Assessment Report for the Post-Authorisation Measure P46 017

Fycompa Post Authorisation Safety Study final report (E2007-G000-402):

A Global, Post marketing Observational Safety Study to Evaluate the Long-Term Safety and Tolerability of Fycompa® (Perampanel) as Add-on Therapy in Epilepsy Patients Aged ≥ 12 Years- completed

International non-proprietary name: perampanel

Product No. EMEA/H/C/002434

Marketing authorisation holder: Eisai Limited

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1. Introduction

Study E2007-G000-402, “Study 402” is an Eisai-sponsored Phase 4 post-approval safety study (PASS). The Committee for Medicinal Products for Human Use (CHMP) had requested Eisai to conduct a PASS as a source of additional safety data for identified safety risks and missing safety information. Therefore, Study 402 was designed as an observational, cohort study to evaluate the safety profile of perampanel when prescribed as add-on therapy in subjects with epilepsy, to assess these adverse events (AEs) under conditions of common (real-life) use in the epilepsy population.

Study 402 was recently completed (last patient last visit [LPLV] was 01 March 2018). The study aimed to evaluate AEs of interest in the categories of important identified risks, important potential risks, and important missing information from the risk management plan. The objective of the study was to address the need for additional safety information on adverse events (AEs) of interest in the categories of important identified risks, important potential risks, and important missing information in the Committee for Medicinal Products for Human Use (CHMP)-approved EU Risk Management Plan (RMP) for perampanel given as add-on therapy in patients with epilepsy. This was achieved by assessment of events of dizziness, blurred vision, somnolence, aggression, balance disorders, ataxia, falls, unintended pregnancy, weight gain, suicidality, drug abuse, misuse, dependence, withdrawal, off-label use, skin photosensitivity, unintended pregnancy while taking levonorgestrel-containing contraceptives, and outcomes associated with any suspected drug-drug interaction.

In addition it was the intention that the study would show any difference in the adverse event profile of the drug in patients not studied at the time of licensing. Specific analysis was requested of patients with cardiovascular disease, a history of psychotic disorder or suicidal behaviour, previous exposure to vigabatrin, history of substance abuse, elderly patients (aged over 65), patients with renal disease, patients with respiratory disease.

The probability of observing events of interest was calculated based on having 500 subjects in the planned final analysis. This number has not been achieved. A total of 483 patients have been included in the safety analysis set. The data collection was started in June 2014 and the agreed final study report date has been revised several times in annual study progress reports because of slower than expected recruitment. This report assesses the final study report findings and includes responses to the RFI submitted in January 2018 to the final interim study report.

2. Summary of data submitted

A total of 493 subjects were treated. Of these, 243 (49.3%) subjects completed the study, an additional 23 subjects completed at least 52 weeks of treatment and were recorded as ongoing on treatment due to failure to reconsent beyond 52 weeks, and 227 (46.0%) subjects discontinued before reaching 52 weeks of treatment.

The mean age (SD) of subjects was 38.3 (15.10) years. The study population was balanced with regard to gender (male, 51.6%) and the majority were white (95.6%). The mean (SD) time since diagnosis was 23 (14.8) years, with the majority of subjects having a complex partial seizure type (56.5%), followed by secondary generalised tonic-clonic (48.7%). Most subjects were taking 1 to 3 concomitant antiepileptic (AEDs).

Of the 483 subjects included in the Safety Analysis Set, 301 (62.3%) reported at least 1 treatment emergent adverse event (TEAE), the majority of which were mild to moderate in severity. A total of 153 (31.7%) subjects had a TEAE of special interest: the most common (≥ 1% incidence) being dizziness (13.9%), balance disorders (5.6%), aggression (5.4%), weight gain

(5.4%), depression events (3.3%), somnolence (2.7%), suicidality (2.1%), events associated with suspected drug-drug interaction (1.7%), and blurred vision (1.4%).

The frequencies of TEAEs of interest reported was generally lower than the incidence observed in clinical studies, with the exception of increases in the incidence of suicidality (2.1% compared to 1.0%) and aggression (5.4% compared to 5.1%). Both these events are labelled in the SmPC.

The majority of events overall had a frequency that was generally similar or lower than the incidence observed in clinical studies.

Events that occurred with an incidence of greater than or equal to 0.5% compared to clinical studies include seizure (7.0% compared to 5.7% [convulsion]), sedation (1.7% compared to 1.0%), epilepsy (1.2% compared to 0.5%), personality disorder (1.2% compared to 0.2%), generalized tonic-clonic seizure (1.0% compared to 0.5% [grand mal convulsion]), nightmare (0.8% compared to 0%), and petit mal-epilepsy (0.6% compared to 0%). Differences in the observed incidence may be due to the way in which events were reported compared to clinical studies.

The frequency of depression was slightly lower than the expected incidence observed in clinical studies. There were a total of 16 events related to depression. Most depression events were non-serious, and mild to moderate in severity, and considered to be related to treatment by the investigator. The exposure adjusted event rate for all terms related to depression events showed no increase in the rate of reactions compared to clinical studies.

All 16 subjects were taking at least 1 concomitant AED medication. Overall, the mean total HADS score for anxiety and depression were similar at Baseline compared to EOS and there was no change in the exposure adjusted event rate for depression compared to clinical studies of the study drug.

Extent of Exposure

All subjects included in the Safety Analysis Set had at least 1 dose of study drug and at least 1 postbaseline safety assessment. The mean (SD) duration of exposure was 38 (22.1) weeks. A total of 472 (97.7%) subjects were exposed for more than 1 week, 319 (66.0%) subjects for more than 26 weeks, and 169 (35.0%) subjects for at least 52 weeks. The mean (SD) daily dose was 4.62 (1.82) mg/day. The mean (SD) maximum dose was 6.0 (2.45) mg. A total of 212 (43.9%) subjects had a mean daily dose less than 4 mg/day, 252 (52.2%) subjects had a mean daily dose between 4 and less than 8 mg/day, and 19 (3.9%) subjects had a mean daily dose between 8 and less than 12 mg/day. No subjects had a mean daily dose greater than or equal to 12 mg/day.

Adverse Events

Of the 483 subjects included in the Safety Analysis Set, 301 (62.3%) reported at least 1 TEAE, 256 (85.0%) of which had TEAEs that were mild to moderate in severity. There were 265 (54.9%) subjects who had at least 1 TEAE considered to be possibly or probably related to study drug by the investigator. A total of 51 (10.6%) subjects had a serious TEAE, of which 2 (0.4%) subjects had a fatal outcome, and 49 (10.1%) subjects had other SAEs. A total of 136 (28.2%) subjects had a TEAE that led to treatment discontinuation.

Table 1 presents all reported TEAEs occurring in ≥2% of subjects during the study by Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PT). The system organ classes (SOCs) with the highest incidence of TEAEs were nervous system disorders (34%), psychiatric disorders (24.4%), and general disorders and administration site conditions (13.7%). The majority of events in these SOCs were of mild to moderate severity.

The TEAEs with the highest incidence were dizziness (13.9%), fatigue (9.5%), seizure (7.0%), irritability (6.2%), and weight increased (5.4%). All of the events of dizziness, fatigue, and irritability were considered as treatment related by the investigator, as well as most of the events of weight increased (5.0%) and approximately half of the events of seizure (3.7%).

Table 1 Treatment-Emergent Adverse Events Occurring in ≥2% of Subjects by Decreasing Frequency by Preferred Term – Safety Analysis Set

MedDRA PT	Study Drug (N=483) n (%)
Subjects with any TEAE	301 (62.3)
Dizziness	67 (13.9)
Fatigue	46 (9.5)
Seizure	34 (7.0)
Irritability	30 (6.2)
Weight increased	26 (5.4)
Aggression	22 (4.6)
Vertigo	21 (4.3)
Balance disorder	14 (2.9)
Somnolence	13 (2.7)
Headache	12 (2.5)
Depression	10 (2.1)
Gait disturbance	10 (2.1)

MedDRA Version 20.1.
A TEAE is defined as an AE that emerged during treatment, up to 30 days after the date of last dose, having been absent at pretreatment (Baseline) or reemerged during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or worsened in severity during treatment relative to the pretreatment state, when the AE was continuous. Subject with two or more adverse events with the same preferred term is counted only once for that preferred term.
AE = adverse event, MedDRA = Medical Dictionary for Regulatory Activities, N = total number of subjects in treatment group, n = number of subjects in individual group, PT = preferred term, SOC = system organ class, TEAE = treatment-emergent adverse event.
Source: Table 14.3.1.2.3.

The frequencies of TEAEs reported was generally lower than or similar to the incidence observed in clinical studies. Events that occurred at a higher rate with an incidence of greater than or equal to 0.5% compared to clinical studies include seizure (7.0% compared to 5.7% [convulsion]), aggression (4.6% compared to 3.7%), sedation (1.7% compared to 1.0%), suicidal ideation (1.4% compared to 0.7%), epilepsy (1.2% compared to 0.5%), personality disorder (1.2% compared to 0.2%), generalized tonic-clonic seizure (1.0% compared to 0.5% [grand mal convulsion]), nightmare (0.8% compared to 0%), and petit mal-epilepsy (0.6% compared to 0%).

There were 2 deaths observed during the study. The primary cause of death in one was malignant brain oedema in a 37 year old male with a history of status epilepticus, and in the other was sudden unexplained death in epilepsy (SUDEP) in a 16 year old male. Both cases were assessed by the treating physicians as not related to treatment.

Fifty one (10.6%) subjects experienced at least 1 AE that met the criteria for serious. The highest incidence of SAEs by SOC was nervous system disorders (5.8%) followed by psychiatric disorders (2.5%). SAEs occurring in more than 1 subject were seizure (2.1%), status epilepticus

(0.8%), generalized tonic-clonic seizures (0.6%), suicide attempt (0.6%), ataxia (0.4%), psychotic disorder (0.4%), intentional overdose (0.4%), pneumonia (0.4%), and epilepsy (0.4%). All serious generalized tonic clonic seizures, suicide attempt, ataxia, psychotic disorder events and intentional overdose as well as some events of seizure (0.8%) and some events of status epilepticus (0.4%) were considered related to treatment by the investigator.

TEAEs resulting in discontinuation of study drug or interruption of study drug and/or dose adjustment occurred in 136 (28.2%) subjects and 101 (20.9%) subjects in the Safety Analysis Set, respectively. The highest incidence of TEAEs resulting in treatment discontinuation or interruption of study drug and/or dose adjustment by SOC was nervous system disorders (14.5% and 11.4%, respectively), psychiatric disorders (12.4% and 7.7%, respectively), and general disorders and administration site conditions (5.0% and 4.3%, respectively). The most common (>2% incidence) TEAEs leading to treatment discontinuation were dizziness (5.4%), seizure (3.5%), aggression (3.3%), fatigue (3.3%), and irritability (2.1%). The most common (≥1% incidence) TEAEs resulting in interruption of study drug and/or dose adjustment were dizziness (5.6%), irritability (3.1%), fatigue (2.9%), vertigo (1.9%), seizure (1.9%), gait disturbance (1.0%), and balance disorder (1.0%).

Two subjects reported a TEAE of accidental overdose that was not associated with another TEAE in either subject, and 2 subjects reported a TEAE of intentional overdose that was associated with a TEAE of suicide attempt in both subjects. These events were assessed as probably related and possibly related to study drug by the investigator, respectively. There were 25 (5.2%) subjects who were prescribed study drug, but who did not have partial seizures with or without secondary generalization in medical history or at treatment initiation; however, the majority of these subjects had primary generalized tonic-clonic seizures, for which the study drug was approved during the course of the study. Other indications included generalized seizures, unclassified epileptic seizures and infantile spasms, Lennox gastaut syndrome, and atypical Dravet syndrome. A total of 4 (0.8%) subjects used study drug off label as monotherapy at any time during the study. Of these 4 subjects, 3 were prescribed study drug as monotherapy at Baseline and continued on monotherapy throughout the course of the study, and 1 received study drug as monotherapy for 2 days between discontinuation of 1 AED and initiation of a different AED.

One pregnancy was reported for a woman in the Safety Analysis Set exposed to study drug in the study. The subject underwent an induced abortion and there was no interruption or change in the dose of study drug.

Adverse events of special interest

A total of 153 (31.7%) subjects had a TEAE of special interest, the most common (≥1% incidence) being dizziness (13.9%), balance disorders (5.6%), aggression (5.4%), weight gain (5.4%), depression events (3.3%), somnolence (2.7%), suicidality (2.1%), outcomes associated with suspected drug-drug interaction (1.7%), and blurred vision (1.4%). The frequencies of TEAEs of interest reported was generally lower than the incidence observed in clinical studies, with the exception of increases in the incidence of suicidality (2.1% compared to 1.0%) and aggression (5.4% compared to 5.1%). There were 8 subjects with events considered related to a drug-drug interaction. All events occurred in single subjects except for fatigue which occurred in 2 subjects (0.4%). The interacting medications in all reports were other AEDs. The majority of events were moderate in severity and non-serious with 2 serious events reported.

All events of dizziness and aggression were considered related to treatment by the investigator. Most events related to balance disorders (includes terms of balance disorder, ataxia, and fall) and weight gain were considered to be related to treatment by the investigator; only 1 (0.2%) event of balance disorder, 2 (0.4%) events of fall and 2 (0.4%) events of weight increased were considered to be not related. All events of suicidality and most events of somnolence and depression were considered to be related to treatment by the investigator; only 1 (0.2%) event

each of somnolence and depression were considered to be not related. While most TEAEs of special interest were of mild to moderate severity, 4 (0.8%) events of dizziness, 1 (0.2%) event of aggression, 1 (0.2%) event of somnolence, 2 (0.4%) events of balance disorder, 1 (0.2%) event of ataxia, 1 (0.2%) event of suicidal ideation, and 3 (0.6%) events of suicide attempt were severe.

TEAEs of interest were reported in at least 1 subject in the subgroup of subjects with cardiovascular disease, hypertension, congestive heart failure, history of myocardial infarction, or any evidence of risk factors for QT prolongation (14 [42.4%] subjects); subjects exposed to vigabatrin (6 [40.0%] subjects); subjects ≥65 years with epilepsy (11 [44%] subjects); subjects with a history of drug or alcohol dependency (3 [75%] subjects); subjects who were pregnant or lactating (1 [100.0%] subject); subjects with renal disease (3 [42.9%] subjects); and subjects with underlying liver disease (2 [40.0%] subjects). While the incidence of some events was higher in some subgroups compared to subjects not in the subgroup, the groups are too small to provide any meaningful assessment, with most events occurring in 1 or 2 subjects. There were no TEAEs of special interest reported by subjects in any other subgroup, including subjects with a history of psychotic disorder or suicidal behaviour in the previous 2 years, subjects with a history of substance abuse, and subjects with respiratory disease.

The frequency of depression events reported was slightly lower than the incidence observed in clinical studies (3.3% compared to 4.0%).There were a total of 16 events related to depression: 10 events of depression, 4 events of depressed mood, and 1 event each of decreased interest and postictal depression. Most depression events were non-serious, and mild to moderate in severity; only 1 (6.3%) event of depression met the criteria of serious and only 2 (12.5%) events of depression were severe. Of these 3 events, all resulted in subject withdrawal from the study. Of the 16 depression events reported, 8 (50%) events resulted in subject withdrawal from the study, 5 (31.3%) events resulted in dose reduction, 2 (12.5%) events required no action, and the action taken for 1 (6.3%) event was unknown.

Most depression events were considered to be related to treatment by the investigator; only 1 (6.3%) event of depression and 1 (6.3%) of postictal depression were considered to be unrelated to treatment by the investigator.

The exposure adjusted event rate for all terms related to depression events show no increase in the rate of reactions compared to clinical studies.

Subject Subgroups

Table 2 : Subject Subgroups identified as important missing information at the RMP

Category	Study Drug (N=483) n (%)
Subjects with cardiovascular disease, hypertension, congestive heart failure, history of myocardial infarction, or any evidence of risk factors for QT prolongation	33 (6.8)
Subjects with a history of psychotic disorder or suicide behavior in the previous 2 years	2 (0.4)
Subjects exposed to vigabatrin	15 (3.1)
Subjects with a history of substance abuse	0
Elderly subjects (≥65 years) with epilepsy	25 (5.2)
Subjects with a history of drug or alcohol dependency	4 (0.8)
Subjects who are pregnant or lactating	1 (0.2)
Subjects with renal disease	7 (1.4)
Subjects with respiratory disease	0
Subjects with underlying liver disease	5 (1.0)

Percentages are based on the total number of subjects with non-missing values.
N = total number of subjects in treatment group, n = number of subjects in individual group.

Of the 33 subjects in the subgroup of subjects with cardiovascular disease, hypertension, congestive heart failure, history of myocardial infarction, or any evidence of risk factors for QT prolongation, 14 (42.4%) subjects reported at least 1 event of special interest TEAEs reported were, dizziness 4 (12.1%) subjects, balance disorders 4 (12.1%) subjects, weight gain 3 (9.1%) subjects, aggression 2 (6.1%) subjects, blurred vision 1 (3.0%) subject, somnolence 1 (3.0%) subject, suicidality 1 (3.0%) subject, and depression events 1 (3.0%) subject.

Of the 15 subjects in the subgroup of subjects exposed to vigabatrin, 6 (40.0%) subjects reported at least 1 event of special interest (Table 14.3.2.6.1.3). TEAEs reported were dizziness 2 (13.3%) subjects, aggression 2 (13.3%) subjects, weight gain 2 (13.3%) subjects and somnolence 1 (6.7%) subject.

Of the 25 subjects in the subgroup of subjects ⩾65 years with epilepsy, 11 (44%) subjects reported at least 1 event of special interest (Table 14.3.2.6.1.5). TEAEs reported were dizziness 6 (24.0%) subjects, balance disorders 3 (12.0%) subjects, somnolence 2 (8.0%) subjects, weight gain 1 (4.0%) subject, suicidality 1 (4.0%) subject, and depression events 1 (4.0%) subject.

Of the 4 subjects in the subgroup of subjects with a history of drug or alcohol dependency, 3 (75%) subjects reported at least 1 event of special interest (Table 14.3.2.6.1.6). TEAEs reported were weight gain 2 (50.0) subjects, aggression 1 (25.0%) subject, suicidality 1 (25.0) subject, and depression events 1 (25.0) subject.

There was 1 subject in the subgroup of subjects who were pregnant or lactating and this subject reported the following TEAEs of special interest; unintended pregnancy while taking levonorgestrel-containing contraceptives, suicidality, and depression events. Due to the inclusion of a single subject in this subgroup, no clinical conclusions can be made.

Of the 7 subjects in the subgroup of subjects with renal disease, 3 (42.9%) subjects reported at least 1 event of special interest. TEAEs reported were, dizziness (28.6%) subjects, and weight gain 1 (14.3%) subject.

Of the 5 subjects in the subgroup of subjects with underlying liver disease, 1 subject reported dizziness and 1 reported weight gain.

Subset numbers are very small. There are no reactions in any subsets of patients of interest identified at the RMP that are significantly different to those for the general study population but the small numbers makes interpretation of this observation very limited.

Efficacy Results
Of the 483 subjects in the Safety Analysis Set who had a CGI-C assessment, 44.6% noted improvement (4.8% of subjects had very much improved disease severity, 21.2% of subjects had much improved disease severity, 18.6% of subjects had minimally improved disease severity), 34% of the subjects had no change in disease severity, and 21.5% noted worsening (11.3% of subjects had minimally worse disease severity, 9.2% of subjects had much worse disease severity, and 1.0% of subjects had very much worse disease severity) compared to baseline.

3. Scientific discussion

In the 483 patients in the safety analysis set, the frequencies of TEAEs did not differ significantly from that reported in clinical trials with some notable exceptions of labelled reactions- aggression and suicidal ideation and unlabelled events of seizure and related terms that could be due to lack of efficacy and the baseline risk in the patient population with epilepsy. The two deaths are not considered to be related to perampanel but related to the underlying disease.

The frequency of TEAEs of special interest were generally lower than the incidence observed in clinical studies, with the exception of increases in the incidence of suicidality (2.1% compared to 1.0%) and aggression (5.4% compared to 5.1%).

The frequency of depression events reported was slightly lower than the incidence observed in clinical studies (3.3% compared to 4.0%). Suicidality is labelled in the SmPC for perampanel and there is advice in section 4.4 to monitor mood although this is in the context of a warning on aggression. There were a total of 16 events related to depression: 10 events of depression, 4 events of depressed mood, and 1 event each of decreased interest and postictal depression. Most depression events were non-serious, and mild to moderate in severity; only 1 (6.3%) event of depression met the criteria of serious and only 2 (12.5%) events of depression were severe. Of these 3 events, all resulted in subject withdrawal from the study.

Of the 16 depression events reported, 8 (50%) events resulted in subject withdrawal from the study, 5 (31.3%) events resulted in dose reduction, 2 (12.5%) events required no action, and the action taken for 1 (6.3%) event was unknown.

Most depression events were considered to be related to treatment by the investigator; only 1 (6.3%) event of depression and 1 (6.3%) of postictal depression were considered to be unrelated to treatment by the investigator. The exposure adjusted event rate for all terms related to depression events show no increase in the rate of reactions compared to clinical studies. The 16 subjects reporting depression events were aged between 23 to 69 years old and the majority were female (68.8%). All 16 subjects were taking at least 1 concomitant AED medication including, levetiracetam (8 subjects), lamotrigine (5 subjects), clobazam (4 subjects), carbamazepine (4 subjects), lacosamide (3 subjects), eslicarbazepin (3 subjects), zonisamide (2 subjects), topiramate (2 subjects), oxcarbazepine (2 subjects), and clonazepam, pregabalin, phenytoin, and valproic acid. Of the 16 subjects reporting ongoing depression events, 5 subjects had a history of depression events: 4 subjects with history of depression and 1 subject with a history of adjustment disorder with depressed mood. In addition, there was 1 subject with an

ongoing history of anxiety. Of the 16 subjects reporting depression events, 4 subjects additionally reported events of suicidal ideation, 1 subject additionally reported events of intentional overdose and suicide attempt, and 2 subjects reported anxiety.

Of the 8 depression events resulting in withdrawal, 4 subjects had increased total HADS scores (anxiety and depression scores); 1 subject had an increased total depression score and reduced total anxiety score, 1 subject had an increased total anxiety score and stable total depression score, and 1 subject had stable total anxiety score and decreased total depression score at the EOS Visit compared to baseline. The remaining subject did not have available HADS data at the EOS, but presented with normal total scores (both anxiety and depression) at Baseline.

Of the 5 depression events resulting in a dose reduction, 1 subject had increased total HADS scores (anxiety and depression scores), 1 subject had decreased total HADS scores (anxiety and depression scores), and 1 subject had increased total anxiety score and reduced total depression score at the EOS compared to Baseline. The remaining 2 subjects did not have PASS Report E2007-G000-402 HADS data available at the EOS; 1 subject presented at Baseline with a mild depression and 1 subject additionally did not have Baseline HADS data.

Of the 2 events requiring no action 1 subject had increased total HADS scores (anxiety and depression scores) and 1 subject had increased total anxiety score and reduced total depression score at the EOS compared to Baseline. The remaining 2 subjects did not have HADS data available at the EOS; 1 subject presented at Baseline with a mild depression and 1 subject additionally did not have Baseline HADS data.

Implications of the cases of depression for labelling are not discussed by the MAH. The 16 cases from the PASS are either confounded by other medications or a psychiatric history. The cases are assessed in the context of the prevalence of mood disorders in patients with epilepsy which is known to be increased. The currently available data in the PASS are insufficient for labelling depression but the issue of depression, low mood and related terms will continue to be closely monitored at PSUSAs. The class risk of suicidality is labelled in the SmPC without the labelling of depression.

Events that are reported with a greater frequency than clinical trial data include suicidality (including terms suicidal ideation, intentional drug overdose and suicide attempt)- in clinical studies frequency was 1.0% and in this study Study 402, a slight increase (1.1%) was noted with an incidence of 2.1%. The incidence of aggression (including terms aggression, anger and paranoia) in clinical studies was 5.1% and in this study slightly increased at 5.4%. Suicidality and aggression are adequately labelled in the SmPC and there are no risk factors identified in the line listings of cases in the PASS data that would warrant additional pharmacovigilance activity.

The MAH reports that 23 subjects had missing data because they did not consent for use of data beyond 52 weeks. Where off label use is reported there were 25 (5.2%) subjects who did not have partial seizures with or without secondary generalisation that used study drug in this study, however, the majority of these subjects had primary generalized tonic-clonic seizures, for which the study drug was approved during the course of the study. Other indications included generalized seizures, unclassified epileptic seizures and infantile spasms, Lennox gastaut syndrome, and atypical Dravet syndrome. A total of 4 (0.8%) subjects used study drug off-label as monotherapy at any point in the study. The study findings cannot be reliably generalised to patients receiving perampanel monotherapy (not an EU authorised indication at the time of study) due to this small number of patients.

There are very small numbers of patients in the subgroups of interest and no conclusions can be made as a result. There were no patients with respiratory disease and no patients with a history

of substance abuse. The largest number of patients is in the subgroup with cardiovascular disease. The types of adverse events in these patients were similar to adverse events in the general population but with 33 patients in this group no firm conclusions on the significance of this can be drawn.

3. Overall conclusion

The study hasn't achieved its aim of better characterising use in patients in various risk groups, due to the small number of patients recruited making interpretation of the findings difficult. The agreed number (500 patients) required to power the study to observe the AEs of interest was not reached. However in the safety analysis inclusion of 483 patients findings are reassuring that there are no adverse events that are not labelled occurring above the frequency observed in clinical trial data.

There are a high number of patients who discontinued treatment due to adverse events in the dataset presented as well as a high proportion of off label use; and where this is known perampanel is being used for Dravet's syndrome or as monotherapy .

Where data are available there are no concerns that the adverse event profile of perampanel is different in patients with any of the risk factors of interest (cardiovascular disease, patients with a history of psychotic disorder or suicidal behaviour, those exposed to vigabatrin, patient over 65 years, patients with renal disease). There are no patients with respiratory disease or substance abuse in the study so no conclusion can be drawn.

All the subgroups of interest must remain as missing information in the RMP. The serious adverse events that are possibly related to treatment are either already listed (ataxia, aggression, irritability) or the subject of a recent cumulative review in the PSUSA (psychosis, confusion) and remain under close monitoring. Depression should remain under close monitoring at PSUSAs given the number of cases and the labelling of suicidal behaviour and importance of monitoring mood in the context of aggression.

☒ **PAM fulfilled (all commitments fulfilled) - No further action required**