Medical Team Leader Review

Date	04/26/2016
From	Eisai Co.
Subject	Clinical Team Leader
NDA/BLA # Supplement#	208-277
Applicant	Eisai Inc.
Date of Submission	06/30/2015
PDUFA Goal Date	04/30/2016
Proprietary Name / Established (USAN) names	Fycompa Perampanel
Dosage forms / Strength	Fycompa oral suspension 0.5 mg/mL
Proposed Indication(s)	1. Adjunctive Treatment of with Partial Onset Seizures(POS) in Patients (b)(4) 12 years of age 2. Adjunctive Treatment of with Primary Generalized Tonic Clonic (PGTC) Seizures in Patients (b)(4) 12 years of age
Recommended:	Approval

1. Introduction/Background

Perampanel is a non-competitive AMPA receptor antagonist developed by Eisai. Based upon prior adequately controlled trials Fycompa tablets was approved on 10/22/12 for adjunctive treatment of partial onset seizures (POS) and later on 6/19/15 for adjunctive treatment of primary generalized tonic clinic (PGTC) seizures, both in patients 12 years of age and older. The present application provides a request for the approval of a Fycompa oral suspension (0.5 mg/ml) formulation for the same indications and at the same dosages as is presently labeled for the tablets based upon a pharmacokinetic comparison of this new formulation to the presently marketed tablet. Because clinical pharmacology is the predominate data relied on for approval the Clinical Pharmacology Team Leader, Angela Men, is serving as the CDTL.

2. CMC/Device

The quality review was performed by S. McLamore, K. Janoria, P Krieger, R. Xu, O. Anand, D. Woody, and M. Heiman. They note that "from a quality perspective, NDA 208277 for Fycompa® (perampanel) oral suspension is recommended for approval." They do not recommend any postmarketing commitments or requirements.

Also noted in this review is that because the manufacturing process is a low risk process and the firm provided sufficient in-process controls, no PAI is necessary. Thus the site was found acceptable based on the inspection history.

3. Nonclinical Pharmacology/Toxicology

No new data and none required.

4. Clinical Pharmacology/Biopharmaceutics

The OCP reviewer was Dr. X. Yang. Drs. K. Krudys and A. Men were the Team Leaders from this division. Dr. Men, as noted above, served as the CDTL. OCP noted that in fasting state a single dose of the presently marketed tablet and the study suspension where bioequivalent with regard to the Cmax and AUC based upon standard criteria. This was also true for the AUC in the fed state as well. However, the Cmax did not meet bioequivalence standards in the fed state, with a 23% mean reduction in the Cmax of the suspension as compared to the tablet. Based on population pharmacokinetic simulated multiple-dosing scenario analysis at steady state, the AUC and Cmax of perampanel were determined to be bioequivalent when the tablet under fasting conditions was compared to the suspension under the fed state. Because the maintenance therapy at study state is the pertinent issue regarding fed to fasting states OCP concluded that "the oral suspension formulation demonstrated comparable bioavailability as the tablet formulation and can be used interchangeably." This will be noted in the label.

As per the OCP review, the Office of Study Integrity and Surveillance determined that based upon inspection the bioanalytical site, the bioanalytical data of this study are reliable.

OCP recommends approval (see Dr. A. Men's review) and has no additional post marketing commitments or requirements.

5. Clinical Microbiology

P. Krieger performed the microbiology review. She recommended that this submission be approved from the standpoint of microbiology product quality.

6. Clinical/Statistical- Efficacy

Clinical efficacy is concluded and is based upon the prior demonstration of the efficacy of the tablet formulation and the bridging pharmacokinetic studies comparing the tablet and suspension formulations provided in this application.

7. Safety

Safety is concluded and is based upon the prior demonstration of the safety of the tablet formulation and the bridging pharmacokinetic studies comparing the tablet and suspension formulations provided in this application. Safety data, from the pharmacokinetic studies, was reviewed in this application as well.

Exposures and numbers of patients examined in the present pharmacokinetic studies are substantially less than those that led to approval of the tablets. The new safety data submitted in these pharmacokinetic studies, however, were reviewed by Dr. Getzoff, DNP Clinical Review.

Safety data from the following two studies were reviewed:

- Study E2007-E044-028 (Study 028): a randomized, open-label, 2-period, 2-sequence crossover study that compared the relative bioavailability of a single 4 mg dose of perampanel oral suspension to a single 4 mg dose of perampanel tablet (reference formulation) in healthy adult subjects (n=16) under fasted conditions.

- Study E2007-A001-048 (Study 048): an open-label, 2 arm (tablet and oral suspension), single-dose, randomized crossover bioequivalence study that compared a single 12 mg dose of the tablet to the suspension formulation under fasted (Arm 1, n=50) and a single 12 mg dose of the tablet and suspension formulation under fed (high-fat meal) conditions (Arm 2, n=50) in healthy adult subjects.

Subjects in the above studies received two single doses of formulations separated by a wash out period. In study 48, 94 received the tablet formulation, and 95 received the oral suspension. In study 28, 15 received both formulations.

No Deaths were observed.

Dr. Getzoff notes that a single serious adverse event (SAE) occurred in Study 048 that was described as a spontaneous abortion. The subject was a 23-year-old female, who was noted to have a positive pregnancy test at the check-in visit for Treatment Period 2 (Day 42) and was not administered the second dose of perampanel (OS). On Day 52, the subject presented to the ER with vaginal bleeding. She had "low" beta-human chorionic gonadotropin levels, and an ultrasound was performed in the ER, which detected no pregnancy. The investigator was unable to rule out the possibility that the event was related to the study drug. Little can be concluded from this single case of a single dose exposure. Chronic exposures in animals, however, have been associated with fetal death. (b) (4)

Dr. Getzoff notes that there were no adverse events resulting in treatment withdrawal, discontinuation of the study drug, or study drug adjustment in either study. However, it should be noted that the above adverse SAE resulted in exclusion from receiving a second dose. This was discussed with Dr. Getzoff who agrees that this represents a single case of withdrawal because of an adverse event

Dr. Getzoff notes that there were no incidences of adverse events from allergic reaction (including rash and hypersensitivity), suicidality, or drug induced liver injury.

Although, the predominant determination of safety is based upon prior studies bridged through the present PK studies, a brief summary of common adverse events are discussed below.

Of the 16 patients studied in Study 28, 13 subjects reported 26 TEAEs during the conduct of the study. This study was too small to provide any new information regarding the difference between tablet and liquid formulation. Nonetheless, no new obvious adverse event suggested a definitive new signal. Of note there was a high incidence of the reporting of gastroenteritis during for both the tablet and suspension, with 4 of15 and 3 of 16 cases noted for the suspension and tablet, respectively. It is difficult to conclude anything from this because of the limited number of subjects and the fact that this study was performed at a single site. Headache and dizziness was also common. These two adverse events are labeled as common adverse events.

Seventy-four subjects (74%) of the 100 patients studied experienced a treatment emergent adverse event in Study 048 at the studied dose of 12 mg. All adverse events observed in this study are presented in the table below (transcribed from Dr. Getzoff's review). This was a relatively short study, with relatively short exposures. But, in general it does not appear that tablet and solution differed with regard to occurrence of common adverse events. The events presented here are similar to that described in the label and with similar relative rates; e.g., dizziness, somnolence, headache and nausea were observed at high rates compared to other adverse events. Euphoric Mood was also observed and is noted in the label.

Table 6: TEAEs in ≥ 5% of Subjects in Any Treatment Group During the Treatment Phase by SOC and PT (Safety Analysis Set, Study 048)

MedDRA System Organ Class Preferred Term	Treatment A (Tablet/fasted) (N=49)	Treatment B (OS/fasted) (N=48)	Treatment C (Tablet/fed) (N=45)	Treatment D (OS/fed) (N=47)	Overall (N=100)
Subjects with any TEAE	**36 (73.5)**	**31 (64.6)**	**26 (57.8)**	**24 (51.1)**	**74 (74.0)**
Ear and labyrinth disorders	**3 (6.1)**	**2 (4.2)**	**2 (4.4)**	**0 (0)**	**7 (7.0)**
Vertigo	3 (6.1)	2 (4.2)	2 (4.4)	0 (0)	7 (7.0)
Gastrointestinal disorders	**14 (28.6)**	**6 (12.5)**	**4 (8.9)**	**2 (4.3)**	**22 (22.0)**
Dry mouth	3 (6.1)	0 (0)	0 (0)	0 (0)	3 (3.0)
Nausea	5 (10.2)	4 (8.3)	2 (4.4)	0 (0)	9 (9.0)
Paraesthesia oral	6 (12.2)	2 (4.2)	0 (0)	0 (0)	6 (6.0)
General disorders and administration site conditions	**4 (8.2)**	**2 (4.2)**	**1 (2.2)**	**4 (8.5)**	**11 (11.0)**
Infections and infestations	**2 (4.1)**	**1 (2.1)**	**1 (2.2)**	**1 (2.1)**	**5 (5.0)**
Nervous system disorders	**31 (63.3)**	**28 (58.3)**	**24 (53.3)**	**18 (38.3)**	**63 (63.0)**
Dizziness	22 (44.9)	19 (39.6)	14 (31.1)	7 (14.9)	41 (41.0)
Headaches	5 (10.2)	7 (14.6)	1 (2.2)	1 (2.1)	12 (12.0)
Somnolence	12 (24.5)	10 (20.8)	16 (35.6)	14 (29.8)	39 (39.0)
Psychiatric disorders	**3 (6.1)**	**3 (6.3)**	**0 (0)**	**1 (2.1)**	**4 (4.0)**

Source: Study 048, CSR, Table 17 (verified using JMP)
(Highlighted ≥5%)

As this is a new formulation CSS was requested to review the application. As per my opinion no new pertinent dependence or addiction data appear to be included in this application. Dr.

Alicja Lerner performed the review. She recommended that the label provides information in section 5.5 and section 9 that "during the post-marketing period withdrawal convulsions and drug dependence were reported." This recommendation was based upon postmarketing reports of seizures upon withdraw of Fycompa in epilepsy patients, Upon questioning Dr. Lerner she clarified that the description of a drug dependence syndrome is based upon her interpretation that seizures represent withdrawal seizures. Of note, section 5.5 of the label, entitled Withdrawal of Antiepileptic Drugs, presently states "there is the potential of increased seizure frequency in patients with seizure disorders when antiepileptic drugs are withdrawn abruptly," and further states "a gradual withdrawal is generally recommended with antiepileptic drugs, but if withdrawal is a response to adverse events, prompt withdrawal can be considered." It is noteworthy that drug withdrawal in pivotal studies, which were provided in the previously reviewed applications, was performed abruptly; likely because of the very long half-life of this drug (105 hours). In these studies there was insufficient evidence of a seizure withdrawal syndrome. Dr. Lerner requested specific post-marketing information on seizures associated with withdrawal in a 3/9/16 request to the sponsor. Fourteen cases were provided by the sponsor. Dr. Lerner expressed the opinion in a follow-up review that these demonstrated the possibility of the existence of a withdrawal seizure withdrawal syndrome. In her second review she notes that section 9 should provide information describing the "potential for Fycompa to produce withdrawal symptoms," in other parts of this section noting withdrawal convulsions. Neither I nor Dr. Getzoff, after examining the postmarketing cases, believes this data provide proof that such convulsions were a part of a withdrawal syndrome. Seizures upon removal of therapeutic agent may occur simply as a result of reduced treatment. While many of the cases states seizures were increased, it does not note that they necessarily increased over a pre-Fycompa treatment period. Moreover, I do not believe the postmarketing data trumps those from the pivotal controlled trials, which notes that a definitive seizure withdrawal syndrome was not identified in the examination of the phase 3 studies. Lastly, the Sponsor does have a PMR that will more carefully study this issue. While in some respects the PMR study may flawed, as expressed in discussions with Dr. Lerner, as it is examining seizure patients, I believe with careful observation, it has the potential to answer the question of wither there is a seizure withdrawal syndrome. Also, as noted above, the present label suggests care when withdrawing Fycompa, by its reference to the antiepileptic class of drugs. Following review of the postmarketing cases Dr. Getzoff and I had a teleconference with Dr. Lerner, but we were unable to come to a consensus on this issue. The two Divisions and the Division Directors will meet again, post action, to discuss this issue so as to come to a mutually agreed upon conclusion.

Dr. Lerner has requested that additional information on an animal dependence study[1] be included in the label; this information was provided in prior approval packages. I would concur to this. Dr. Lerner also notes that the Sponsor did not submit to CSS animal studies previously requested (study in rats # ES06156 and juvenile toxicity studies). This action is not part of this submission and CSS should provide a separate inquiry.

[1] "Pre-clinical dependence study in rats showed significant withdrawal symptoms including hyper-reactivity to handling, muscle rigidity, decreases in food consumption and body weights."

No significant EKG or vital sigh change was noted in patients in the two reviewed studies. One case of low neutrophil count was noted following the last dose of drug. This was thought to be potentially a result of a viral illness and not believed to be drug related. A single case as this, against the already large clinical database, is unrevealing.

I agree with Dr. Getzoff that, "there are no clinical safety issues impeding the approval of the proposed product."

One additional safety matter should be noted that is requiring a labeling change. In section 5.1, Serious Psychiatric and Behavioral Reactions, the label presently notes that "in the non-epilepsy trials, psychiatric events that occurred in perampanel-treated patients more often than placebo-treated patients included disorientation, delusion, and paranoia." Because delusions are most notably associated with psychosis, and a potential signal for psychosis was identified in a pediatric review by DPV, Dr. K. Long of DPV, performed a postmarketing review of the FAERS database and literature for neuropsychiatric adverse events. She identified 32 cases of psychosis or delirium that suggest a causal association with perampanel. She notes

> All 32 cases reported a temporal relationship with a median time to onset of 30 days, and 25 cases reported a positive dechallenge. Twenty-nine cases reported a serious outcome, including 16 hospitalizations. More than half of the cases (17 of 32) required treatment in a medical facility, with 9 cases reporting the use of an antipsychotic or benzodiazepine.

She also further notes:

> Both the perampanel-treated groups and the phase 3 placebo groups reported neuropsychiatric adverse events related to psychosis or delirium, however, some events were reported only in the perampanel-treated group (i.e., psychotic disorder, delirium, hallucination auditory, paranoia, and acute psychosis). The phase 2 placebo groups did not report neuropsychiatric adverse events related to psychosis or delirium. Lastly, the disproportionality analysis for perampanel with events related to psychosis or delirium (psychotic disorder, acute psychosis, hallucinations, psychotic behavior, and confusional state) revealed an EB05 score of ≥ 2, suggesting a potential association.

Moreover, Dr. Long further notes that:

> Non-epilepsy doubleblind pooled studies reported the following adverse events in perampanel-treated groups that were not reported in the placebo groups: paranoia, hallucination auditory, acute psychosis.

This led Dr. Long to believe that causality was likely and severity was sufficient to require the adding of this information to section 5.1.

She recommends that the following be added:

> In the postmarketing setting, there have been reports of psychosis (acute psychosis, hallucinations, delusions, paranoia) and delirium (delirium, confusional state, disorientation, memory impairment) in patients treated with perampanel.

I agree with this. In particular, I believe that the combination of the very clear signal for delusions in normal subjects from the clinical trial, knowing the association of delusional behavior and psychosis, and the strong post marketing signal for psychosis requires our recommended labeling.

8. Advisory Committee Meeting

None necessary.

9. Pediatrics

Dr. Getzoff notes a number of PREA PMRs in her review. Except for one (see below), these represent old PMRs for the tablets. Because of a change in policy regarding pediatric extrapolation the division is no longer requesting a controlled efficacy/safety trial for labeling of partial onset seizures in patients 4 years to 12 years old, but allows extrapolation from adults with adequate PK data. We, however, continue to request open-label safety data in this population. We will therefore specify in a new PMR for this safety data as follows:

> A long-term, open-label, safety study of adjunctive therapy in patients 1 month to < 12 years with epilepsy: The purpose of this study is to evaluate the long-term safety of perampanel as adjunctive therapy in the treatment of partial-onset seizures (ages 1 month to < 12 years) or primary generalized tonic-clonic seizures in pediatric patients (ages 2 to < 12 years). Doses for this study must be at or above those doses determined to be efficacious by Study 1932-4 (patients 1 month to < 4 years old with partial-onset seizures), Study 2922-1 (patients 2 to < 12 years with primary generalized tonic-clonic seizures), and the pharmacokinetic analyses used for the extrapolation of efficacy in pediatric patients 4 to < 12 years with partial-onset seizures. This study may include subjects enrolled in the extension phases of Studies 1932-1, 1932-2, 1932-4, and 2922-1, and may be supplemented as necessary. A minimum of 100 patients must be exposed to study drug for one year at or above the dose or doses identified as effective. Subjects should be balanced among age cohorts to allow for adequate conclusions to be drawn.

This PMR was agreed upon by PeRC. (b) (4) [redacted]

10. Other Relevant Regulatory Issues

- Financial disclosures: Dr. Getzoff examined the financial disclosure information for study E2007-A001-048 and notes that there were no financial disclosable arrangement, and concludes there that no financial arrangements "introduced significant bias into the results of this trial."

11. Labeling

See above and final agreed upon label.

12. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Approval.

- Risk Benefit Assessment: No new safety issues for this formulation were identified. OCP determined that this formulation can be interchangeably used with that of the tablet.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies: None required.

- Recommendation for other Postmarketing Requirements and Commitments: The only postmarketing issue identified by the team was the PREA PMR, noted above.

- Recommended Comments to Applicant: The Clinical Team has none.

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/s/

NORMAN HERSHKOWITZ
04/28/2016