

Summary Review

Date	September 27, 2018
From	Philip H. Sheridan, MD
Subject	Summary Review
NDA/BLA # and Supplement#	202834 (S-014); 208277 (S-002) 202834 ((S-015), 208277 (S-003)
Applicant	Eisai, Inc.
Date of Submission	March 28, 2018
PDUFA Goal Date	September 28, 2018
Proprietary Name	Fycompa
Established or Proper Name	Perampanel
Dosage Form(s)	Tablets and Oral Suspension
Applicant Proposed Indication(s)/Population(s)	Treatment of partial onset seizures with or without secondarily generalized seizures in patients with epilepsy 2 years of age and older Treatment of primary generalized tonic-clonic seizures in patients with epilepsy 2 years of age and older
Applicant Proposed Dosing Regimen(s)	8-12 mg QD
Recommendation on Regulatory Action	Approval for the treatment of partial onset seizures with or without secondarily generalized seizures in patients with epilepsy 4 years of age and older

1. Background

Perampanel was originally approved for adjunctive treatment of partial onset seizures (POS) in patients 12 years of age and older on October 22, 2012. This approval was based on the results of three controlled efficacy trials. Perampanel was subsequently approved for adjunctive treatment of primary generalized tonic-clonic seizures (PGTC) in patients 12 years of age and older on June 19, 2015, based on a single controlled efficacy trial. An oral suspension formulation was approved for use in these same indications on April 29, 2016. Perampanel was also approved for use as monotherapy in patients 12 years of age and older with partial onset seizures on July 26, 2017. This approval was based on extrapolation of efficacy using pharmacokinetic analyses of data previously included in the original NDA 202834 submission.

This supplemental application seeks to extend the current pediatric indications based on extrapolation of efficacy from adult patients to pediatric patients, as follows:

- Treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy 2 years of age and older (current indication for partial-onset seizures is for adjunctive or monotherapy use in patients 12 years of age and older)
- Treatment of primary generalized tonic-clonic seizures in patients with epilepsy 2 years of age and older (current indication for primary generalized tonic-clonic seizures is adjunctive therapy in patients 12 years of age and older)

The Division of Neurology Products (DNP) issued a General Advice letter on November 12, 2015, indicating that it would be acceptable to extrapolate to pediatric patients 4 years of age and older the effectiveness of drugs approved for the treatment of POS in adults. This determination was based on the similarity of POS in pediatric patients 4 years of age and older and in adults and on an analysis of multiple antiepileptic drugs, conducted by FDA, that demonstrated a similar exposure-response relationship in pediatric and adult patients with POS. Extrapolation based on this analysis originally applied only to POS in pediatric patients 4 years of age and older, and not to POS in pediatric patients 1 month of age to less than 4 years of age or to other forms of epilepsy. The following has been required to support an indication for the treatment of POS in patients 4 years and older that relies upon extrapolation:

- Approved indication for the treatment of POS in adults.
- A pharmacokinetic analysis to determine a dosing regimen that provides similar drug exposure (at levels demonstrated to be effective in adults) in pediatric patients 4 years of age and older and in adult patients with POS. This analysis requires pharmacokinetic data from both the adult and pediatric (4 years of age and older) populations.
- Long-term open-label safety study(ies) in pediatric patients 4 years of age and older.

Additionally, DNP issued a General Advice letter on September 13, 2016, indicating that it is acceptable to extrapolate monotherapy use of a drug approved as adjunctive use for the treatment of POS. To support use as monotherapy for the treatment of POS based on extrapolation, the proposed dosages of a drug, when used as monotherapy, should result in exposures that are similar to those demonstrated to be safe and effective when the drug is used as adjunctive therapy for the treatment of POS. To support extrapolation, the sponsor must

provide pharmacokinetic information adequate to demonstrate such similarity, taking into consideration possible drug-drug interactions (inhibition or induction) that may alter the metabolism of the drug.

More recently, DNP has concluded that POS in patients 2 years to less than 4 years of age are sufficiently similar to POS in older children and in adults to allow extrapolation of efficacy down to 2 years of age, provided that a pharmacokinetic analysis can identify a dosing regimen that provides similar drug exposure (at levels demonstrated to be effective in adults) in pediatric patients 2 years of age and older and in adult patients with POS, and that sufficient information is available to support the safety of the product in pediatric patients 2 years of age and older.

There are currently no sufficient data to support pediatric extrapolation, or extrapolation from adjunctive therapy to monotherapy, for primary generalized tonic-clonic seizures.

The regulatory history of perampanel is reviewed in detail in the clinical review by Dr. Natalie Getzoff.

2. Product Quality

No new product quality information was submitted.

3. Nonclinical Pharmacology/Toxicology

No new nonclinical information was included or required for this submission.

4. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) review was performed by Michael Bewernitz and Dawei Li, with Kevin Krudys and Angela Men as Team Leaders.

As noted above, perampanel is already approved for adjunctive and monotherapy use as treatment for partial onset seizures in patients 12 years and older. It is also approved for adjunctive treatment of primary generalized tonic-clonic seizures in patients 12 years and older.

To support the proposed indication for adjunctive and monotherapy use in treatment of POS in patients 2 to less than 12 years of age, the applicant provided pediatric pharmacokinetic (PK) data from two open-label, single-arm studies in patients with refractory epilepsy:

- Study E2007-G000-232 (Study 232): an open-label, single-arm study in 50 patients 2 to less than 12 years of age with various types of epilepsy (including POS, PGTC, and Lennox-Gastaut syndrome), intended to evaluate PK and generate preliminary safety,

efficacy, and tolerability data for perampanel oral suspension as adjunctive therapy in pediatric patients with epilepsy. These data were used to inform the dosing in Study 311.

- Study E2007-G000-311 (Study 311): a multi-center, open-label, single-arm study in 157 patients 4 to less than 12 years of age with POS or PGTC, intended to evaluate the PK, safety, and tolerability of perampanel oral suspension as adjunctive therapy in pediatric patients with inadequately controlled seizures.

The current submission proposes efficacy extrapolation from adult patients to pediatric patients for POS and PGTC seizures, and extrapolation from adjunctive therapy to monotherapy for PGTC seizures.

Partial onset seizures

- 1) Extrapolating perampanel adjunctive therapy from adults to children 2 years of age and older for POS:

The applicant provided a pharmacokinetic analysis to determine a dosing regimen that would provide similar perampanel exposure (at levels demonstrated to be effective in adults) in pediatric subjects 2 years of age and older and in adult subjects with POS. Based on review of the data, OCP has concluded that the applicant has only provided data adequate to support a dosing regimen that would provide similar perampanel exposure in pediatric patients 4 years of age and older. Perampanel pharmacokinetics do not appear to scale with weight between age 4 and older ages, which indicates that adults and children 4 years of age and older can have the same dosing recommendations.

The number of patients from 2 years to less than 4 years of age was insufficient to reliably assess pharmacokinetics in this age group; in addition, these patients received a maintenance dose level less than a third of the minimum proposed maintenance dose level. Therefore, additional PK data in patients from 2 years to less than 4 years of age will be needed before dosing recommendations can be made for that age group. A postmarketing requirement (PMR) will be issued to obtain these data.

- 2) Extrapolating perampanel monotherapy from adjunctive therapy in children for the treatment of POS:

To support use of perampanel as monotherapy for the treatment of POS based on extrapolation, the proposed dosages of a drug, when used as monotherapy, should result in exposures that are similar to those demonstrated to be safe and effective when the drug is used as adjunctive therapy for the treatment of POS. The approved perampanel labeling recommends a greater starting dosage (4 mg with concomitant moderate or strong CYP3A4 inducers versus 2 mg without these inducers) for patients 12 years of age and older. The same dosage recommendations can be applied to patients 4 years of age and older, for the reasons noted above.

The Clinical Pharmacology reviewers propose the dosing regimen shown in **Table 1** for pediatric patients with POS.

Table 1: Perampanel Dosage Schedule for Pediatric Patients Age 4 to 17 Years with POS

Concomitant Medication Status	Initial Dosage	Titration Step	Minimum and Maximum Maintenance Dosage
With concomitant use of moderate or strong 3A4 inducers	4 mg once daily	Increase by 2 mg, no more frequently than once a week	12 mg once daily
Without concomitant use of moderate or strong 3A4 inducers	2 mg once daily	Increase by 2 mg, no more frequently than once a week	8 to 12 mg once daily

Since the oral suspension and oral tablet have comparable bioavailability, the dosing recommendations for the tablet are also applicable to the oral suspension.

Primary generalized tonic-clonic seizures

For primary generalized tonic-clonic (PGTC) seizures, the acceptability of extrapolation in a manner similar to that used for POS is not established, as there is currently insufficient information to support extrapolation of efficacy from adult to pediatric patients, or from adjunctive therapy to monotherapy, for PGTC seizures. The applicant included a discussion of disease similarity and a presentation of a meta-analysis of 3 drugs approved for PGTC seizures based on the published literature. This information is much more limited than that relied upon by the Agency to support extrapolation in POS and is insufficient to independently establish the acceptability of extrapolation in PGTC seizures. In addition to the small number of drugs available for consideration, the applicant was not able to conduct and present reviews of the effectiveness of the considered drugs based on primary data, nor was the applicant able to conduct quantitative analyses of exposure-response for the presented drugs, let alone other drugs for which data may be available. Such analyses are critical to this issue and were of primary importance in establishing the acceptability of extrapolation in POS. Notably, FDA has previously considered the issue of PGTC seizures extrapolation using similar internal analyses as those performed for POS extrapolation, and has concluded to this point that the existing data are not sufficient to support such an analysis. Finally, as an alternative to extrapolation, we note that the applicant has not provided primary efficacy data establishing the effectiveness of perampanel for the population for which approval is sought. Thus, in the absence of information adequate to support pediatric extrapolation or extrapolation from adjunctive therapy to monotherapy for PGTC seizures, this application does not support modifications to the currently approved PGTC seizures indication for perampanel.

5. Clinical Microbiology

Not applicable.

6. Clinical/Statistical- Efficacy

Evidence for the effectiveness of perampanel in patients with POS aged 4 to less than 12 years is based on the prior demonstration of efficacy in patients aged 12 years and above with POS. The pharmacokinetic analyses described above support the conclusion that the same dosing recommendations can be applied to all age groups from age 4 years through adulthood.

Additionally, evidence for the effectiveness of monotherapy use of perampanel for the treatment of POS in patients from 4 years to less than 12 years of age is based on the prior demonstration of efficacy when used as adjunctive therapy for the treatment of POS in patients 12 years and above and the expectation of similar exposures with monotherapy or adjunctive use of perampanel. Refer to Section 4 for a more detailed discussion of these analyses.

7. Safety

The safety data in this submission were reviewed by Natalie Getzoff.

As described in Dr. Getzoff's review, the primary sources of safety data were from Study 232 and Study 311 (see Section 4 of this summary review for a description of the studies).

The total number of pediatric patients 2 to less than 12 years of age who were exposed to perampanel in Studies 232 and 311 was 230 (including patients enrolled into Study 311 after the original data cutoff and included in the 120-day safety update).

The sponsor performed safety analyses on Studies 311 and 232 separately. However, all FDA analyses were performed on the integrated pooled dataset submitted on July 13, 2018, which included 207 patients who had been exposed to perampanel during Studies 311 and 232. The FDA safety analyses pooled safety data from the core and extension phases from both studies.

There was 1 death during Studies 311 and 232. The cause of death (viral myocarditis) was not attributable to the study drug.

The overall incidence of treatment-emergent serious adverse events (TESAEs) was 14.5% in the perampanel-treated patients. The most-commonly reported TESAE was seizures (4.3%). Each remaining TESAE was reported by 1 or 2 patients. The overall SAE rate in patients taking perampanel in the adjunctive controlled POS trials was 5.5%, and 5.0% in the placebo group. The TESAE rate in the entire epilepsy study pool in the original NDA safety review (including the controlled trials and the open-label long-term extension studies) was 17%, slightly higher than the 14.5% seen in pooled open-label pediatric Studies 311 and 232. Only

5 patients discontinued treatment due to a TESAE. The types of TESAEs reported in Studies 311 and 232 were similar to those in the controlled POS studies in older patients.

A total of 24 patients (11.6%) discontinued perampanel due to any TEAE (serious and nonserious) in Studies 311 and 232, which was slightly higher than that seen in the patients taking perampanel in the controlled POS trials (8.4%) in older patients. Dr Getzoff notes that the reason for this higher rate is unclear, but, as there was no control group for comparison, further conclusions cannot be drawn. The most common causes of discontinuation due to TEAE were irritability (1.9%), seizure/convulsion (1.9%), and aggression (1.4%). Discontinuations due to TEAEs were more likely to occur earlier in the treatment, with 58% occurring during the titration period.

Certain adverse events of special interest were specifically evaluated. TEAEs related to hostility or aggression were of special interest due to the greater incidence seen in patients taking perampanel in the controlled POS trials in older patients. Overall, hostility- and aggression-related TEAEs were reported in 31% patients in Studies 311 and 232. The most common TEAEs in this category were irritability (13%), aggression (10%), agitation (5%), and abnormal behavior (3%). Two-thirds of the hostility- or aggression-related TEAEs occurred in the older age group (7 to < 12 years). This finding, although complicated by the lack of a control group and small population, suggests that these behavioral effects may be more prominent in older children. Three of these events were reported as SAEs (aggression, abnormal behavior, and disruptive mood dysregulation disorder), two of which led to discontinuation; five of the events were characterized as severe. Hostility- or aggression-related TEAEs led to drug discontinuation in nine patients, and dose reduction in 24 patients. As in the controlled trials in older patients, hostility- and aggression-related TEAEs occurred in a sizable minority of patients, leading to discontinuation or dose reduction, supporting the continued need for the warning in labeling. However, these findings are similar to those seen in older patients and do not raise any new clinical concerns.

Rash occurred in 14% of patients, leading to discontinuation in one patient. No patients reported an SAE related to rash.

Four patients were reported as exhibiting suicidality (3 with suicidal ideation and 1 with suicidal ideation and behavior). Only one patient was discontinued from the drug due to suicidality, and one had a dosage reduction. None of these cases was deemed serious or severe. The rate of suicidality (1.9%) was greater than that in controlled POS trials in older patients (0.3%). Potential reasons for this include enrollment of patients with significant underlying behavioral problems, overestimation due to the small sample size, and careful attention to suicidality during the studies. These findings do not raise new clinical concerns.

There were no cases of drug-induced liver injury. No patient met Hy's law criteria. Three patients had ALT or AST > 2 x ULN. No patients discontinued treatment due to LFT abnormalities or liver dysfunction. A total of 8 patients (3.9%) had transient mildly or moderately abnormal hematology abnormalities; all of these patients recovered completely, and none required perampanel discontinuation.

TEAEs occurred in 86% of patients in Studies 311 and 232. The most common TEAEs overall in Studies 311 and 232 were somnolence (23%), nasopharyngitis (19%), pyrexia (15%), rash (14%), irritability (13%), dizziness and vertigo (13%), vomiting (13%), upper respiratory tract infection (13%), aggression/anger (12%), seizures (11%), and ear infection (10%). These TEAEs are similar to those seen in controlled clinical trials in older patients. The occurrence of common pediatric infections is not unusual in open-label pediatric trials. These findings raise no new safety concerns.

In summary, review of the safety data from the studies of perampanel in pediatric patients with epilepsy demonstrated no new safety signals. The safety profile was generally consistent with that seen in adolescents and adults.

8. Advisory Committee Meeting

None required.

9. Pediatrics

The submission was discussed with the Pediatric Review Committee. A listing of PREA PMRs released and reissued is given in section 13 below.

10. Other Relevant Regulatory Issues

No Good Clinical Practice (GCP) issues were identified in Dr. Getzoff's clinical review.

Dr. Getzoff concludes that the applicant has adequately disclosed financial interests or arrangements with clinical investigators.

11. Labeling

Please refer to the final negotiated product label. Labeling negotiations with the applicant have been completed and the applicant has accepted all recommended changes.

12. Risk Benefit Assessment

The applicant has provided substantial evidence of effectiveness for the monotherapy and adjunctive use of perampanel in pediatric patients aged 4 to less than 12 years with POS based on the prior findings of effectiveness of perampanel in the population aged 12 years and above and pharmacokinetic analyses that support the conclusion that the same dosing

recommendations can be applied to all age groups from age 4 years of age through adulthood. There are no new safety concerns identified with the use of perampanel in patients aged 4 to less than 12 years. There are no outstanding unresolved issues.

Two Pediatric Research Equity Act (PREA) postmarketing requirements (1932-4 and 3076-1) have been partially addressed by studies conducted with perampanel tablets and oral suspension in the age group of 4 to less than 12 years, and are being replaced by new PMRs (3496-1 and 3496-2) for the age group of at least 1 month to less than 4 years. Another postmarketing requirement (1932-9) is no longer needed because agreed-upon language has been added to Section 9.3 (Dependence) of the Fycompa Prescribing Information (as discussed in Section 13 below). A comprehensive and detailed update of the current status of postmarketing requirements is provided in Section 13 below.

The applicant has provided insufficient information to support the proposed changes to the primary generalized tonic-clonic seizures indication of perampanel.

Specific postmarketing risk management activities are not needed.

We have agreed with the sponsor on product labeling that describes the effectiveness and safety of perampanel for the treatment of partial onset seizures in patients aged 4 to less than 12 years.

13. Postmarketing Recommendations

The following is an abridged version of the text from the approval letter updating the current status of the postmarketing requirements.

RELEASE FROM POSTMARKETING REQUIREMENT

We note that these supplements contain study reports that are responsive to the following postmarketing requirements listed in our October 22, 2012, and April 29, 2016, approval letters, for Fycompa tablets (NDA 202834) and Fycompa oral suspension (NDA 208277), respectively.

1932-4 Deferred pediatric study under PREA: A prospective, randomized, controlled, double-blind, efficacy and safety study of FYCOMPA (perampanel) for the adjunctive treatment of partial onset seizures in children ages 1 month to < 4 years with a long term safety extension. The primary efficacy endpoint during the controlled phase will examine seizure frequency based upon Video/EEG data. Safety will be evaluated during the controlled phase and long term extension.

- 3076-1 A long-term, open-label, safety study of adjunctive therapy in patients from 1 month to less than 12 years of age with epilepsy. The purpose of this study is to evaluate the long-term safety of FYCOMPA (perampanel) as adjunctive therapy in the treatment of partial-onset seizures (ages 1 month to less than 12 years) or primary generalized tonic-clonic seizures in pediatric patients (ages 2 to less than 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 less than 4 years of age with partial-onset seizures), Study 2922-1 (patients 2 to less than 12 years of age with primary generalized tonic-clonic seizures), and the pharmacokinetic analyses used for the extrapolation of efficacy in pediatric patients 4 to less than 12 years of age 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.
- 1932-9 A prospective human physical dependence trial in patients. The subjects should be titrated to the approved therapeutic dose of FYCOMPA (perampanel) of 8-12 mg, and maintained at this dose for an appropriate amount of time. At the end of the treatment, the drug should be abruptly withdrawn. The trial should be adequately designed to allow differentiation of direct drug toxicity from true withdrawal symptoms.

We have reviewed your submissions and have determined that you are released from the above postmarketing requirements for the following reasons:

1. The Pediatric Research Equity Act (PREA) postmarketing requirements (1932-4 and 3076-1) have been partially addressed by studies conducted with Fycompa tablets and oral suspension in the age group of 4 to less than 12 years and will be reissued for the age group of at least 1 month to less than 4 years for these two dosage forms.
2. The postmarketing requirement (1932-9) is no longer needed because the following language has been added to Section 9.3 (Dependence) of the Fycompa Prescribing Information (per the agreement noted in the December 15, 2017, Preliminary Comments):

FYCOMPA may cause dependence and withdrawal symptoms that may include anxiety, nervousness, irritability, fatigue, lethargy, asthenia, mood swings, and insomnia.

Postmarketing requirements 1932-4 and 3076-1 are being replaced by the new postmarketing requirements (3496-1 and 3496-2) described below. Additionally, with the approval of these supplements (NDA 202834/S-014, NDA 208277/S-002), Fycompa tablets and oral suspension are appropriately labeled for use in pediatric patients aged 4 years to less than 12 years.

REQUIRED PEDIATRIC ASSESSMENTS

Under the PREA (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Your deferred pediatric studies required under section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(C) of the FDCA. These required studies are listed below.

3496-1 Deferred pediatric study under PREA: A prospective, randomized, controlled, double-blind, efficacy and safety study of FYCOMPA (perampanel) for the adjunctive treatment of partial onset seizures in children ages 1 month to < 2 years with a long term safety extension. The primary efficacy endpoint during the controlled phase will examine seizure frequency based upon Video/EEG data. Safety will be evaluated during the controlled phase and long term extension. In the long term extension component, a minimum of 25 patients must be exposed to perampanel for 6 months at or above the dose or doses identified as effective.

3496-2 A pharmacokinetic (PK) study in children with epilepsy who are 2 years to less than 4 years of age to characterize pharmacokinetic parameters following multiple administrations of oral perampanel. This study should include patients taking perampanel with and without concomitant CYP3A4 inducers.

Finally, we remind you that there are postmarketing requirements listed in the October 22, 2012, and April 29, 2016, approval letters, for Fycompa tablets (NDA 202834) and Fycompa oral suspension (NDA 208277), respectively, that remain open:

1932-1 A pharmacokinetic study in pediatric patients with partial-onset seizures aged 1 month to < 24 months. At least 2 maintenance dose levels of FYCOMPA (perampanel) should be evaluated to characterize pharmacokinetic parameters following multiple administration of oral perampanel. Pharmacokinetic data can be obtained and analyzed using either conventional pharmacokinetics methods with intensive sampling or using a population PK approach by collecting sparse samples. Subjects should be balanced among age cohorts. Effort should also be made to balance the gender distributions within each age cohort.

1932-8 A prospective, multiple dose, randomized, controlled, double-blind, safety and efficacy trial of FYCOMPA (perampanel) as adjunctive treatment of partial onset seizures when high doses of Fycompa are added to concomitant treatments in adults on CYP34A inducing antiepileptic drugs (phenytoin,

carbamazepine, and oxcarbazepine). The trial will include a long term safety extension. Safety will be evaluated during the controlled phase and long term extension. Safety endpoints will include serious psychiatric and behavioral reactions, and neurologic effects. The efficacy endpoint during the controlled phase will examine seizure frequency based upon diary data. Trial dosages must be selected to produce exposure similar to that experienced by patients receiving 8 and 12 mg of FYCOMPA (perampanel) daily who were on non-inducing concomitant anti-epileptic drugs.

14. Recommended Comments to the Applicant

See action letter.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PHILIP H SHERIDAN
09/27/2018

WILLIAM H Dunn
09/27/2018