Brief Clinical Review and Evaluation of Labeling Supplement and FAERS Report

NDA (Serial Number)	**202834(S-012)**
Sponsor:	**Eisai**
Drug:	**Fycompa (perampanel)**
Indication:	**Adjunctive therapy for the treatment of POS with or without secondarily generalized seizures or PGTC Seizures in patients with epilepsy 12 years of age or older**
Material Reviewed:	**Labeling supplement, FAERS case report**
Date Received / Agency:	**4/27/17**
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Date Review Completed:	**7/19/17**
Reviewer:	**Natalie Getzoff, MD**

1. Introduction

This submission, a labeling supplement to NDA 202834 and 208277, contains a summary of proposed addition of monotherapy treatment with Fycompa tablets or oral suspension for patients ≥ 12 years of age with partial onset seizures (POS). The submission contains no new efficacy data for review and no new safety data were provided.

During the course of this review, a case of drug reaction with eosinophilia and systemic symptoms (DRESS) in a patient who was taking Fycompa tablets was identified in FAERS and reviewed. This brief clinical review evaluates the FAERS case report.

2. Review of DRESS Case

A 10-year-old male from Thailand experienced generalized maculopapular rash, transaminitis, and eosinophilia and was diagnosed with DRESS three days after receiving perampanel for seizures. He was on concomitant phenobarbital, valproate, levetiracetam, and topiramate and was hospitalized for seizures. He started Fycompa 4 mg QD on 8 Feb 2017. On (b) (6), he developed a generalized maculopapular rash, transaminitis and eosinophilia, which prolonged hospitalization and were initially considered to be unrelated to Fycompa. He also was diagnosed with concomitant acute kidney injury and pseudomonas UTI. All AEDs were discontinued and symptoms improved after administration of corticosteroids. Levetiracetam was restarted 5 days later and perampanel was restarted 9 days later. Three days after perampanel and seven days after levetiracetam were resumed, the patient developed symptoms of DRESS again. Both perampanel and levetiracetam were again discontinued, and symptoms were resolving. Perampanel was restarted again 18 days later, and 4 days later the patient again developed symptoms of DRESS. Perampanel was discontinued for the third time and the patient recovered.

One other case of DRESS with a possible causal relationship to perampanel has been reported in the literature, which was the impetus for addition of DRESS to Section 6.2 of the labeling. In that case, a 13 year old girl was hospitalized for DRESS confirmed by skin punch biopsy. The event occurred 59 days after perampanel initiation and resolved after discontinuation and treatment with methylprednisolone, IV immunoglobulin, and a 6 month steroid taper. All concomitant AEDs (perampanel, valproic acid, and lamotrigine) were discontinued. Medical history included intractable epilepsy, focal seizures, cerebral palsy, hemiparesis, and encephalopathy. The causal relationship of DRESS to perampanel in this case was confounded by concomitant medications which are labeled for DRESS (lamotrigine and valproic acid, both received for 2 years). The concomitant drugs and the single case were the primary reasons why DRESS was not added to Warnings and Precautions in 2015.

Reviewer's Comments: A 10 year old boy developed DRESS shortly after starting perampanel. This was a serious adverse event, causing prolonged hospitalization and requiring steroid treatment. The patient had 2 positive dechallenges and 1 positive rechallenge, while on concomitant AEDs, and one subsequent positive rechallenge and dechallenge without concomitant AEDs. Based on the proximate time-to-onset of the event and positive dechallenges/rechallenges (some in the setting of concomitant drugs and some not), there is a probable causal relationship between this case of DRESS and perampanel administration.

3. Recommendation:

Addition of drug reaction with eosinophilia and systemic symptoms (DRESS) to the Warnings and Precautions section of the package insert labeling. DRESS is currently listed in Section 6.2 (Postmarket Experience).There have been two serious cases of DRESS reported with probable causal relationship to perampanel (Fycompa). The most recent case was associated with a prolonged hospitalization, a proximate time to onset, two dechallenges/rechallenges, and one rechallenge/dechallenge occurring without concomitant drugs. Because of the seriousness of both cases of DRESS and the reasonable evidence of a causal relationship between perampanel administration and development of DRESS, DRESS should be included in the Warnings and Precautions section of the labeling.

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/s/

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07/24/2017

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07/25/2017