CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202834Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Management Review

Date:	October 2, 2012
Reviewer(s):	Kendra Worthy, Pharm. D., Team Leader, Division of Risk Management (DRISK)
Division Director	Claudia Manzo, Pharm. D., DRISK
Drug Name(s):	Fycompa (perampanel) Tablets 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg
Therapeutic Class:	Selective non-competitive antagonist of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor
Indication(s):	Treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older
Application Type/Number:	NDA 202834
Applicant:	Eisai, Inc.

INTRODUCTION

This review documents the Division of Risk Management's (DRISK) evaluation of the need for a risk management strategy for permapanel.

An application for Fycompa (permapanel) NDA 202834 was resubmitted to the Division of Neurology Products (DNP) by Eisai, Inc. on December 22, 2011 after receiving a Refuse to File (RTF) letter on July 21, 2011 for the NDA initially submitted May 25, 2011. Even though the Applicant did not propose a risk evaluation and mitigation strategy (REMS), DRISK was consulted by the Division of Neurology Products for participation in the approval process because the proposed drug is a new molecular entity (NME).

Perampanel is a selective, non-competitive antagonist of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor. It is proposed for adult patients for the treatment of partial onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.

1.1 MATERIALS REVIEWED

- Midcycle review slides
- Clinical reviews by Lara Dimick-Santos, M.D., FACS. and Erica Wynn, M.D., M.P.H.

1.2 OVERVIEW OF CLINICAL PROGRAM

Perampanel's mechanism of action for its antiepileptic effects has not yet been fully established. The in vitro studies showed properties of perampanel as a noncompetitive AMPA receptor antagonist[1].

Perampanel is rapidly (and completely) absorbed after oral administration with negligible first-pass metabolism and has an average $t_{1/2}$ of 25 hours. It has weak inhibition and induction qualities with certain P450 enzymes. When administered with food, peak plasma concentrations are reduced and delayed by 2 hours compared with dosing in a fasted state.

Efficacy was established in three 19-week, randomized, double-blind, placebo-controlled, multicenter trials in adult and adolescent patients aged 12 years and older with partial-onset seizures with or without secondary generalization that were not adequately controlled with 1 to 3 concomitant AEDs. During a 6-week baseline period, patients were required to have more than five seizures (no seizure-free period exceeding 25 days) despite taking stable doses of at least 1 to 3 AEDs. The primary endpoint was the percent change in seizure frequency per 28 days in the double-blind treatment period from the 6-week baseline period. Data from placebo-controlled and open-label studies demonstrates that clinically meaningful improvement in seizure control, regardless of background

[1] Prescribing Information (draft dated 3-21-12), Fycompa (perampanel) Tablets NDA 202834

therapy, is observed with a once-daily FYCOMPA dose of 4 mg and this benefit is enhanced as the dose is increased to 12 mg/day. Although 8 deaths occurred in perampanel exposed subjects during the epilepsy studies, no deaths related to the drug were reported[1].

1.2.1 Safety Concerns

Neuropsychiatric Events: the proposed label, which is in the latter stages of completion, contains a boxed warning for serious neuropsychiatric events. The draft language is as follows:

(b) (4)

In the clinical trials, neuropsychiatric events were reported more frequently in patients being treated with perampanel than in patients taking placebo. These events included irritability, aggression, anger, and anxiety that occurred in 2% or greater of perampanel treated patients and twice as frequently as in placebo-treated patients. These events occurred in patients with and without prior psychiatric history, prior aggressive behavior, or concomitant use of medications associated with hostility and aggression. Some patients experienced worsening of their pre-existing psychiatric conditions. Patients with active psychotic disorders and unstable recurrent affective disorders were excluded from the clinical trials[1].

Adverse events listed in the Warnings and Precautions section of the draft label include:

- suicidal behavior and ideation
- dizziness and gait disturbance
- somnolence and fatigue
- falls and injuries
- (b) (4)
- abrupt withdrawal of antiepileptic drugs

Suicidal ideation: Suicidal ideation is risk associated with the class of antiepileptic drugs. The draft label recommends that patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Dizziness and gait disturbance: Dose-related dizziness and gait disturbance was the most common adverse event occurring in approximately (b) (4) of perampanel-treated patients compared with (b) (4) of placebo-treated patients in the phase 3 clinical trials. The events occurred most often during the titration phase; serious events occurred only with the perampanel-treated patients (0.3%). Elderly patients had an increased risk of these adverse reactions.

Somnolence and fatigue: These dose-related events, including asthenia and lethargy, occurred in (b) (4) of perampanel-treated patients compared to 7% of placebo patients. The draft label instructs prescribers to advise patients against engaging in hazardous activities requiring mental alertness until the effect of perampanel is known.

Falls and injuries: In the controlled Phase 3 epilepsy clinical trials, falls were reported in 5% of perampanel-treated patients compared with 3% of placebo-treated patients. Falls were serious adverse events and led to discontinuations more frequently in perampanel-treated patients than placebo-treated patients.

Other: Dr. Doi, the clinical safety reviewer, recommends postmarketing surveillance to further investigate the potential risk of tendon and ligament ruptures as well as cholelithiasis and choledocholithiasis[2].

The label will also include a Medication Guide, which will be reviewed under separate cover by the Office of Medical Policy.

2 DISCUSSION

Seizures, abnormal electrical disturbances of the cortical neural networks, are the hallmark symptom of epilepsy. Most AEDs work via mechanisms that decrease neuronal excitability of ion channels (e.g. sodium, calcium, potassium) or increase neuronal inhibition at GABA receptors. There are AEDs of various mechanisms and side effect profiles, as efficacy and tolerability can vary among differing patient populations[3].

[2] Clinical Safety Review, Fycompa (perampanel) Tablets NDA 202834 dated August 22, 2012 by Mary Doi, M.D., M.S.

[3] Sirven, JI., Noe, K., Hoerth, M., Drazowski, J. Antiepileptic Drugs 2012: Recent Advances and Trends. *Mayo Clin Proc*. 2012;87(9):879-889.

Antiepileptic drugs (AEDs) were part of a class REMS (a Medication Guide) to communicate the risk of suicidal behavior and ideation to patients. The Agency determined that the Medication Guides for AEDs were no longer required as an element of a REMS following the publishing of the Guidance on Medication Guides — Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS) (draft March 2011, final November 2011). The Medication Guide remains part of labeling for AEDS.

The current safety profile of perampanel observed during the clinical program is consistent with other AEDs. Dr. Doi in the clinical safety review states that "it is anticipated that toxicities that have not been observed in the premarketing database might be identified once the drug is used in the postmarketing setting, particularly in patients who are not as healthy as those included in the clinical trials"[2].

3 CONCLUSION

DRISK believes that a REMS for Fycompa (perampanel) is not necessary at this time. The risks identified at this time can be managed adequately through labeling and routine pharmacovigilance. Should DNP identify additional safety information that warrants risk mitigation measures, please send a consult to DRISK.

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/s/

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10/02/2012

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