

No.19-01

January 4, 2019
Eisai Co., Ltd.

NEW DRUG APPLICATION FOR PERAMPANEL DESIGNATED FOR PRIORITY REVIEW BY CHINA NATIONAL MEDICAL PRODUCTS ADMINISTRATION FOR ADJUNCTIVE TREATMENT OF PARTIAL ONSET SEIZURES

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced that its in-house discovered and developed antiepileptic drug (AED) perampanel (generic name, product name: Fycompa®), for which a New Drug Application (NDA) was submitted for review as an adjunctive treatment for partial onset seizures in epilepsy patients 12 years of age and older in China in October 2018, has been designated for Priority Review by the National Medical Products Administration (NMPA) due to perampanel's significant clinical benefit compared to existing treatments.

The Priority Review and Approval procedure was implemented by the NMPA in February 2016 with the aim of accelerating research, development and launch of new medicines that have significant clinical value. Under the procedure the period of time until approval is expected to be shortened.

In China, it is estimated that there are approximately 9 million patients with epilepsy, with approximately 60% being affected by partial-onset seizures, and 40% of these patients with partial-onset seizures require adjunctive treatment.¹ As approximately 30% of patients with epilepsy are unable to control their seizures with currently available AEDs,² this is a disease with significant unmet medical need.

Perampanel is a first-in-class AED discovered at Eisai's Tsukuba Research Laboratories. Administered orally once-daily, it is a highly selective, noncompetitive AMPA receptor antagonist that reduces neuronal hyperexcitation associated with seizures by targeting glutamate activity at AMPA receptors on postsynaptic membranes.

Perampanel has been approved in over 55 countries around the world as an adjunctive treatment for partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy 12 years of age and older. In addition, perampanel has been approved in over 50 countries around the world as an adjunctive treatment for primary generalized tonic-clonic seizures in patients with epilepsy 12 years of age and older. In the United States, perampanel is also indicated for monotherapy and adjunctive use in the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy 4 years of age and older.

Eisai considers neurology including epilepsy, a therapeutic area of focus, and is striving to deliver perampanel to patients in China as soon as possible. In pursuit of our mission to provide "seizure freedom" to a greater number of patients living with epilepsy, Eisai seeks to address the diverse needs of, as well as increasing the benefits provided to, patients with epilepsy and their families.

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[Notes to editors]

1. About perampanel (generic name, product name: Fycompa)

Perampanel is a first-in-class AED discovered and developed by Eisai. With epileptic seizures being mediated by the neurotransmitter glutamate, the agent is a highly selective, noncompetitive AMPA receptor antagonist that reduces neuronal hyperexcitation associated with seizures by targeting glutamate activity at AMPA receptors on postsynaptic membranes. Perampanel is available in tablet form to be taken once daily orally at bedtime. In addition, an oral suspension formulation has been approved in the United States.

Perampanel is currently approved in more than 55 countries and territories, including the United States, Japan, in Europe and in Asia as adjunctive treatment for partial-onset seizures (with or without secondarily generalized seizures) in patients with epilepsy 12 years of age and older. In addition, perampanel has been approved in more than 50 countries, including the United States, Japan, in Europe and in Asia for treatment as an adjunctive therapy for primary generalized tonic clonic seizures in patients with epilepsy 12 years of age and older. In the United States, perampanel is also indicated for monotherapy and adjunctive use in the treatment of partial-onset seizures (with or without secondarily generalized seizures) in patients with epilepsy 4 years of age and older.

Furthermore, Eisai is conducting a global Phase III clinical study (Study 338) for the agent in patients with seizures associated with Lennox-Gastaut syndrome. In Japan and Europe, Eisai is conducting a Phase III study in pediatric patients with epilepsy (Study 311) and plans to submit a marketing authorization application in fiscal 2018. Additionally, positive topline results have been obtained in a Phase III study (Study 342) of perampanel as monotherapy in untreated patients with partial-onset seizures 12 years of age and older currently being conducted in Japan on November 2018. Based on these topline results, the company plans to submit a regulatory application in Japan for perampanel as monotherapy during fiscal 2018.

2. About Phase III study (Study 335) upon which the NDA in China was based³

Study title:	A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Perampanel Administered as an Adjunctive Therapy in Subjects with Refractory Partial-onset Seizures
Study population:	710 patients aged 12 years and older who have a diagnosis of epilepsy with partial-onset seizures with or without secondarily generalized seizures receiving one to a maximum of three anti-epileptic drugs
Treatment administered:	Perampanel oral tablets, 4 mg/day, 8 mg/day and 12 mg/day, once daily before bedtime Perampanel-matched placebo oral tablets, once daily before bedtime
Duration of treatment:	Prerandomization Phase: 6 weeks Randomization Phase (treatment): 19 weeks (Titration Period, 6 weeks; Maintenance Period, 13 weeks) Extension Phase: over 10 weeks
Study locations:	Japan, China, South Korea, Australia, Thailand, Malaysia, Taiwan
Primary endpoint:	Percent change in seizure frequency per 28 days during treatment relative to baseline
Results:	The percent change in seizure frequency in the placebo group was -10.8% while in the perampanel (4 mg, 8 mg, 12 mg) groups it was -17.3%, -29.0% and -38.0%, respectively. The difference between perampanel and placebo was statistically significant for the perampanel 8 and 12 mg groups ($p=0.0003$ for 8 mg, $p<0.0001$ for 12 mg).
Adverse events:	The most common adverse events ($\geq 10\%$ in the perampanel arms and greater than placebo) were dizziness (22.7%, 28.6%, 42.2% in the perampanel 4 mg, 8 mg, 12 mg groups respectively and 5.7% for placebo) and somnolence (15.9%, 17.7%, 17.8% in the perampanel 4 mg, 8 mg, 12 mg groups respectively and 13.1% for placebo).

3. About Epilepsy

Epilepsy affects approximately 3.4 million people in the United States, 1 million people in Japan, 6 million people in Europe, 9 million people in China, and approximately 60 million people worldwide. As approximately 30% of patients with epilepsy are unable to control their seizures with currently available AEDs, this is a disease with significant unmet medical need.

Epilepsy is broadly categorized by seizure type, with partial-onset seizures accounting for approximately 60% of epilepsy cases and generalized seizures accounting for approximately 40%. In a partial-onset seizure, an abnormal electrical disturbance occurs in a limited area of the brain, and may subsequently spread throughout the brain, becoming a generalized seizure (known as a secondarily generalized seizure). In a generalized seizure, abnormal electrical disturbances occur throughout the brain, and can be followed by a loss of consciousness or physical symptoms manifested throughout the whole body.

¹ Clinical Guideline 2015 in China

² "The Epilepsies and Seizures: Hope Through Research. What are the epilepsies?" National Institute of Neurological Disorders and Stroke, accessed May 24, 2016, http://www.ninds.nih.gov/disorders/epilepsy/detail_epilepsy.htm#230253109

³ Nishida T., et al. Adjunctive perampanel in partial-onset seizures: Asia-Pacific, randomized phase III study. *Acta Neurol Scand.* 2018; 137:392-399