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Eisai Co., Ltd.

NEW DRUG APPROVAL FOR FYCOMPA®
FOR ADJUNCTIVE TREATMENT OF PARTIAL ONSET SEIZURES IN CHINA

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today that Eisai received a New Drug Approval for its in-house discovered and developed antiepileptic drug (AED) Fycompa® (perampanel) from the China National Medical Products Administration (NMPA) for use in an adjunctive treatment of partial onset seizures (with or without secondarily generalized seizures) in epilepsy patients 12 years of age and older. Fycompa was designated for Priority Review by the NMPA due to its significant clinical benefits compared to existing treatments, and was approved in about 12 months since the submission in September 2018.

In China, it is estimated that there are approximately 9 million patients with epilepsy, approximately 60% of whom being affected by partial-onset seizures. About 40% 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 needs.

Fycompa 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.
Fycompa has been approved in over 60 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, Fycompa has been approved in over 55 countries as an adjunctive treatment for primary generalized tonic-clonic seizures in patients with epilepsy 12 years of age and older. In the United States, Fycompa 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. With this approval of Fycompa in China, Eisai pursues our mission to provide "seizure freedom" to a greater number of patients with epilepsy across the world living. 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 Fycompa (perampanel)

Fycompa 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. Fycompa is available in tablet form to be taken once daily orally at bedtime. In addition, an oral suspension formulation has been approved and marketed in the United States and in Europe.

Fycompa is currently approved in more than 60 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, Fycompa has been approved in more than 55 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, Fycompa 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.

In Japan, a supplementary new drug application has been filed seeking approval of Fycompa for use as monotherapy for partial-onset seizures, treatment for partial-onset seizures in pediatric patients aged 4 years and older, as well as a fine granule formulation. In Europe, an application has been submitted seeking the additional approval of Fycompa for adjunctive use in the treatment of partial-onset seizures (with or without secondarily generalized seizures) or primarily generalized tonic-clonic seizures in pediatric patients with epilepsy.

Furthermore, Eisai is conducting a global Phase III clinical study (Study 338) for the agent in patients with seizures associated with Lennox-Gastaut syndrome.

2. About Phase III clinical studies upon which to obtain approval in China

The approval of Fycompa in China was based on the results of Phase III clinical study (Study 335[3]) conducted in Japan, China, Korea, as well as the results of three Phase III clinical studies (Study 304[4], 305[5], and 306[6]) conducted in Europe and the United States.

Study 335 was conducted to evaluate the efficacy and safety of Fycompa mainly for the patients in Asia region. Furthermore, Studies 304 and 305 included three arms (placebo, Fycompa 8 mg, and 12 mg) and were to evaluate a more extended dose range. The key goal of Study 306 was to identify the minimal effective dose and included four treatment arms (placebo, Fycompa 2 mg, 4 mg, and 8 mg).

These studies were conducted as the multicenter, randomized, double-blind, placebo-controlled, parallel-group study for the patients aged 12 years and older who have a diagnosis of epilepsy with partial-onset seizures receiving one to a maximum of three anti-epileptic drugs. The primary endpoint of Study 335 was the percentage change in seizure frequency. The primary endpoint of Study 304, 305, and 306 for the approval in Europe was the 50% responder rate (percentage of patients achieving a 50% or greater reduction in seizure frequency compared to pre-randomization phase), while for the approval in the U.S. it was the percentage change in seizure frequency. Specifically, the results showed:

1) Study 335

- The percentage changes in seizure frequency shown were: -17.3% (p=0.223), -29.0% (p=0.0003), -38.9% (p<0.00001) in the 4, 8, and 12 mg Fycompa / day groups, respectively, versus -10.8% with placebo.
- The most common three adverse events were dizziness, somnolence, and nasopharyngitis.

2) Study 304

- The 50% responder rates compared to placebo were 37.6% (p=0.0760) and 36.1% (p=0.0914) in the 8 mg and 12 mg Fycompa / day groups, respectively, versus 26.4% with placebo.
- The percentage changes in seizure frequency shown were: 8 mg = -26.3% (p=0.0261), 12 mg = -34.5% (p=0.0158), and placebo = -21.0%.
- The most common six adverse events were dizziness, somnolence, irritability, headache, falls and ataxia.

3) Study 305

- The 50% responder rates compared to placebo were: 33.3% (p=0.0018) and 33.9% (p=0.0006) in the 8 mg and 12 mg Fycompa / day groups, respectively, versus 14.7% with placebo.

- The percentage changes in seizure frequency shown were: 8 mg = -30.5% (p=0.0008), 12 mg = -17.6% (p=0.0105), and placebo = -9.7%.
- The most common four adverse events were dizziness, fatigue, headache, and somnolence.

4) Study 306

- The 50% responder rates compared to placebo were: 20.6% (p=0.4863), 28.5% (p=0.0132), and 34.9% (p=0.0003) in the 2, 4, and 8 mg Fycompa / day groups, respectively, versus 17.9% with placebo.
- The percentage changes in seizure frequency shown were: 2 mg = -13.6% (p=0.4197), 4 mg = -23.3% (p=0.0026), 8 mg = -30.8% (p<0.0001), and placebo = -10.7%.
- The most common three adverse events were dizziness, headache, and somnolence.

3. About Epilepsy

Epilepsy affects approximately 9 million people in China, 6 million people in Europe, 3.4 million people in the United States, 1 million people in Japan, 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.

[4] French JA, et al. Adjunctive perampanel for refractory partial-onset seizures: randomized phase III study 304. *Neurology* 2012; 79, 589-596

[5] French JA, et al. Evaluation of adjunctive perampanel in patients with refractory partial-onset seizures: results of randomized global phase III study 305. *Epilepsia* 2013; 54, 117-125.

[6] Krauss GL, et al. Randomized phase III study 306: adjunctive perampanel for refractory partial-onset seizures. *Neurology* 2012; 78, 1408-1415.