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Eisai Co., Ltd.

ANTI-EPILEPTIC DRUG FYCOMPA® APPROVED IN CHINA AS MONOTHERAPY FOR PARTIAL-ONSET SEIZURES AND PEDIATRIC INDICATION FOR PARTIAL-ONSET SEIZURES

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today that its in-house discovered and developed anti-epileptic drug (AED) Fycompa® (product name in China: 卫克泰®, generic name: perampanel) has obtained two additional approvals as "a monotherapy for partial-onset seizures" and "an adjunctive treatment / a monotherapy for pediatric indication for partial onset seizures in patients with epilepsy 4 years of age and older" in China from the National Medical Products Administration.
Fycompa has already been approved in China as an adjunctive treatment for partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy 12 years of age and older. Through this approval, Fycompa is now available in China as a monotherapy and an adjunctive treatment for partial-onset seizures (with or without secondarily generalized seizures) in patients with epilepsy 4 years of age and older.

The approval covering monotherapy for partial-onset seizures was based on subgroup analysis estimating monotherapy safety and efficacy within clinical studies of Fycompa as adjunctive therapy (Study 304, 305, 306, and 335) conducted globally including the United States, Europe and China on patients ages 12 years and older with partial-onset seizures (with or without secondarily generalized seizures). Additionally, results of a Phase III clinical study (FREEDOM/Study 342) conducted in Japan and South Korea on untreated epilepsy patients ages 12 years to 74 years old with partial-onset seizures (with or without secondarily generalized seizures) were submitted as supplementary safety and efficacy data of Fycompa as monotherapy.
The approval covering partial-onset seizures in pediatric patients was based on the results of a Phase III clinical study (Study 311) of Fycompa as adjunctive therapy conducted globally on pediatric patients (ages 4 to less than 12 years) with inadequately controlled partial-onset seizures or primary generalized tonic-clonic seizures.

In China, it is estimated that there are approximately 9 million patients with epilepsy, and although onset occurs at any age, onset is most common in people aged 18 and younger and the elderly. As approximately 30% of patients with epilepsy are unable to control their seizures with currently available AEDs[1], this is a disease with significant unmet medical needs.

Fycompa is a first-in-class AED and a once-daily tablet discovered at Eisai's Tsukuba Research Laboratories. The agent is a highly selective, noncompetitive AMPA receptor antagonist that reduces neuronal hyper-excitation associated with seizures by targeting glutamate activity at AMPA receptors on postsynaptic membranes.

Eisai considers neurology, including epilepsy, a therapeutic area of focus. With this approval for Fycompa as a monotherapy and pediatric indication for patients with epilepsy 4 years or older in China, Eisai will continue to prioritize the provision of safety information, and pursue its mission to provide "seizure freedom" to a greater number of patients with epilepsy across the world. Eisai seeks to address the diverse needs of, as well as increase the benefits provided to, patients with epilepsy and their families.

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[Notes to editors]

1. About Fycompa (generic name: perampanel)

Fycompa is a first-in-class anti-epileptic agent (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 currently approved in more than 70 countries and territories, including Japan, the United States, China, and other countries in Europe and in Asia 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 more than 70 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 Japan, the United States and China, Fycompa is approved 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 Europe the approved age range is 4 years of age and older for the adjunctive treatment of partial-onset seizures (with or without secondarily generalized seizures) and 7 years of age and older for the treatment as an adjunctive therapy for primary generalized tonic-clonic seizure. Fycompa is available in drug form to be taken once daily orally at bedtime. A tablet and fine granule formulation have been approved in Japan. An oral suspension formulation and tablet have been approved in the United States and Europe. Eisai is conducting development of an injection formulation. To date, Fycompa has been used to treat more than 410,000 patients worldwide across all indications.

2. About the Phase III clinical studies upon which the approval in China covering monotherapy for partial-onset seizures was based

The approval covering monotherapy for Fycompa in China was based on the results of a Phase III clinical study (Study 335[2]) conducted including Japan, China, and South Korea, as well as the subgroup analysis results estimating monotherapy safety and efficacy of three Phase III clinical studies (Study 304[3], 305[4], and 306[5]) conducted globally including the United States, Europe and China.

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 United States; 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% ($p=0.0003$), -38.0% ($p<0.00001$) 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 -26.3% (p=0.0261) and -34.5% (p=0.0158) in the 8 mg and 12 mg Fycompa / day groups, respectively, versus -21.0% with placebo.
- 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 -30.5% (p=0.0008) and -17.6% (p=0.0105) in the 8 mg and 12 mg Fycompa / day groups, respectively, versus -9.7% with placebo.
- 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 -13.6% (p=0.4197), -23.3% (p=0.0026), and -30.8% (p<0.0001), in the 2, 4, and 8 mg Fycompa / day groups, respectively, versus -10.7% with placebo.
- The most common three adverse events were dizziness, headache, and somnolence.

3. About FREEDOM (Study 342)[6]

FREEDOM (Study 342) is an uncontrolled, open-label Phase III clinical study evaluating efficacy and safety for the Fycompa monotherapy conducted in Japan and South Korea on untreated epilepsy patients aged 12 to 74 with partial-onset seizures with or without secondarily generalized seizures. Up to 4 mg of Fycompa was taken orally once daily before bedtime (may be titrated up to 8 mg if seizures occur). This study comprised a treatment phase including a titration period of 6 weeks and a maintenance period of 26 weeks (if titrated up from 4 mg to 8 mg, titration period was 4 weeks and maintenance period was 26 weeks) and an extension phase. In this study, 89 patients were administered Fycompa as monotherapy, and the proportion of 73 patients for evaluation receiving 4 mg who were seizure-free during the treatment period exceeded the efficacy criteria*, and the primary endpoint was met. In addition, the interim results demonstrated that the 4 mg and 8 mg patients combined also exceeded the efficacy criteria. The most common adverse events (incidence of 10% or higher) observed in this study were dizziness, somnolence, nasopharyngitis and headache, which is consistent with the safety profile of Fycompa to date.

*The criteria for efficacy in this study with 73 patients for evaluation of efficacy required a 52.1% or higher proportion of patients to have achieved seizure freedom, which was set primarily in consideration of the results from other AED monotherapy studies.

4. About Study 311[7]

Study 311 is a global (United States, Europe, Japan, South Korea), open-label Phase III clinical study evaluating the safety, tolerability, and exposure efficacy relationship of the Fycompa oral suspension when administered as an adjunctive therapy in 180 pediatric epilepsy patients aged 4 to less than 12 with inadequately controlled partial-onset seizures or primary generalized tonic-clonic seizures. This study comprised a treatment phase including a titration period of up to 11 weeks and a maintenance period of up to 12 weeks and an extension phase. In this study, 2 to 16 mg of Fycompa was taken orally once daily before bedtime. Primary endpoints were safety and tolerability. Efficacy was similar to that observed in patients 12 years of age and older. The most common adverse events (incidence of 10% or higher) observed in this study were somnolence, nasopharyngitis, pyrexia, vomiting, dizziness, influenza, and irritability, which is consistent with the safety profile of Fycompa to date.

5. About Epilepsy

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

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] "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

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

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

[4] 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.

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

[6] Yamamoto, Takamichi et al. Efficacy and safety of perampanel monotherapy in patients with focal-onset seizures with newly diagnosed epilepsy or recurrence of epilepsy after a period of remission: The open-label Study 342 (FREEDOM Study). *Epilepsia*, 2020; 5, 274-284.

[7] Fogarasi, Andras et al. Open-label study to investigate the safety and efficacy of adjunctive perampanel in pediatric patients (4 to <12 years) with inadequately controlled focal seizures or generalized tonic-clonic seizures. *Epilepsia*. 2020; 61, 125-137.