No.15-51

July 27, 2015
Eisai Co., Ltd.

EISAI SUBMITS NEW DRUG APPLICATION IN JAPAN FOR IN-HOUSE-DISCOVERED ANTIEPILEPTIC DRUG PERAMPANEL AS ADJUNCTIVE THERAPY FOR PARTIAL-ONSET AND GENERALIZED TONIC-CLONIC SEIZURES

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today it has submitted a new drug application in Japan for its in-house-discovered antiepileptic drug (AED) perampanel hydrate (generic name, U.S. and Europe brand name: Fycompa®, "perampanel") as an adjunctive therapy for partial-onset and primary generalized tonic-clonic seizures.

This submission utilizes the Pharmaceutical and Medical Devices Agency's prior assessment consultation system to shorten application review time. Eisai had already submitted a part of the submission package, including data from the clinical studies on partial-onset epilepsy conducted in Europe and the United States. For this new drug application, Eisai has submitted additional clinical study data from a clinical study on partial-onset epilepsy conducted in Asia including Japan (Study 335) as well as data from a global clinical study on primary generalized tonic-clonic (PGTC) seizures in patients with generalized epilepsy (Study 332[1]).

Study 335 was a placebo-controlled Phase III clinical study designed to evaluate the efficacy and safety of adjunctive perampanel therapy in patients aged 12 years and older with refractory partial-onset seizures. According to the results of the study, perampanel demonstrated a statistically significant reduction in the study's primary endpoint of seizure frequency at doses of 8 mg/day and 12 mg/day, compared to placebo. Study 332 was a placebo-controlled Phase III clinical study designed to evaluate the efficacy and safety of adjunctive perampanel therapy in patients aged 12 years and older with PGTC seizures. According to the results of the study, perampanel demonstrated a statistically significant reduction in the study's primary endpoint of PGTC seizure frequency compared to placebo, and 30.9% of patients treated with perampanel were free of PGTC seizures during the 13 week maintenance period (12.3% for placebo).
The most common adverse events observed in Study 332 and Study 335 were dizziness, fatigue, headache, somnolence and irritability.

Perampanel is a first-in-class AED discovered and developed by Eisai, available as a once-daily oral dose. The agent is a highly selective, noncompetitive AMPA receptor antagonist that reduces neuronal hyperexcitation associated with seizures by targeting glutamate activity at postsynaptic AMPA receptors. The agent is currently approved in more than 45 countries and territories, including Europe and the United States, as an adjunctive treatment of partial-onset seizures (with or without secondarily generalized seizures) in adult and adolescent patients from 12 years of age with epilepsy, and has been launched under the Fycompa brand name in over 25 countries. Furthermore, perampanel was approved for an indication expansion regarding the adjunctive therapy of PGTC seizures in patients from 12 years of age with generalized epilepsy in the U.S. and Europe in June 2015.

Epilepsy affects approximately 1 million people in Japan. 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%. Primary generalized tonic-clonic seizures are one of the most common and most severe forms of generalized seizures, accounting for approximately 60% of generalized epilepsy and approximately 20% of all epilepsy cases.[2]

As approximately 30% of patients with epilepsy are unable to control their seizures with currently available AEDs,[3] this is a disease with significant unmet medical needs. The generalized tonic-clonic seizures that are covered in the indication for this application are one of the most severe forms of epileptic seizures as they can cause significant injury to patients from falling down suddenly, and the frequency of these seizures is the most important risk factor associated with sudden unexpected death in epilepsy (SUDEP).[4] Eisai considers epilepsy a therapeutic area of focus and by providing multiple treatment options in addition to perampanel as part of an extensive epilepsy product portfolio, Eisai seeks to make continued contributions 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 hydrate (generic name, U.S. and Europe brand name: Fycompa, "perampanel")

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 postsynaptic AMPA receptors.

The agent is currently approved in more than 45 countries and territories, including Europe and the United States, as an adjunctive treatment (available as a once-daily oral dose) of partial-onset seizures (with or without secondarily generalized seizures) in adult and adolescent patients from 12 years of age with epilepsy, and has been launched in over 25 countries.

Applications seeking an additional indication for the adjunctive treatment of primary generalized tonic-clonic (PGTC) seizures in adult and adolescent patients from 12 years of age with generalized epilepsy were filed with regulatory authorities in Europe and the United States in August 2014, and approved in the United States and Europe in June 2015.

Eisai has submitted this regulatory application covering both PGTC seizures and partial-onset seizures based primarily on Study 332 and Study 335 in Japan.

Meanwhile, Eisai has submitted applications for the approval of an additional oral suspension formulation of perampanel in Europe and the United States in June 2015, and is conducting Phase II studies in Europe and the United States for partial-onset epilepsy in pediatric patients.

2. About Study 335

Study title:	A Multicenter, Double-blind, Randomized, 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:	Perampanel demonstrated a statistically significant reduction in seizure frequency at doses of 8 mg/day and 12 mg/day, compared to placebo
Adverse events:	The most common adverse events (>10% in the perampanel arms and greater than placebo) were dizziness and somnolence.

(Detailed results of the study will be presented at an academic conference in the near future.)

3. About Study 332[1]

Study title:	A Multicenter, Double-blind, Randomized, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Adjunctive Perampanel in PGTC Seizures
Study population:	164 patients aged 12 years and older with PGTC seizures receiving one to a maximum of three anti-epileptic drugs
Treatment administered:	(Placebo-controlled) Perampanel oral tablets, once daily, up to 8 mg/day (Titration Period), randomized dose 8 mg/day (Maintenance Period)
Duration of treatment:	Prerandomization Phase (Screening and Baseline Periods): up to 12 weeks Randomization Phase (treatment): 17 weeks (Titration Period, 4 weeks; Maintenance Period, 13 weeks) Extension Phase: over 38 weeks
Study locations:	U.S., Europe, Japan, Asia
Primary endpoint:	Percent change in PGTC seizure frequency (percent change from baseline in PGTC seizure frequency per 28 days during treatment)
Results:	-A reduction in PGTC seizure frequency of 76.5% was observed for perampanel, which was statistically significant when compared to a reduction of 38.4% for placebo ($p<0.0001$). -The responder rate for perampanel was 64.2%, which was a statistically significant improvement over the responder rate (percentage of patients who experience a 50% or greater reduction in PGTC seizure frequency per 28 days in the Maintenance period relative to baseline) for placebo of 39.5% ($p=0.0019$). -For patients who had been unable to adequately control PGTC seizures with existing AEDs, 30.9% of patients treated with perampanel were free of PGTC seizures (12.3% for placebo) during the 13 week Maintenance period.
Adverse events:	The most common adverse events (>10% in the perampanel arm and greater than placebo) for perampanel and placebo were, respectively, dizziness (32.1% vs 6.1%), fatigue (14.8% vs 6.1%), headache (12.3% vs 9.8%), somnolence (11.1% vs 3.7%) and irritability (11.1% vs 2.4%).

4. About Epilepsy

Epilepsy affects approximately 1 million people in Japan, 2.9 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,[3] 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 sometimes 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.

Primary generalized tonic-clonic seizures are one of the most common and most severe forms of generalized seizures, accounting for approximately 60% of generalized epilepsy and approximately 20% of all epilepsy cases.[2]

5. About Generalized Tonic-Clonic Seizures

Generalized tonic-clonic seizures are one of the most severe forms of epileptic seizures as they can cause significant injury to patients from falling down suddenly, and the frequency of these seizures is the most important risk factor associated with sudden unexpected death in epilepsy (SUDEP).[4]

For the majority of patients, a generalized tonic-clonic seizure begins with a loss of consciousness without any prior warning symptoms and a sudden contraction of the tonic muscles, causing the patient to fall down (tonic phase). This is followed by violent convulsions (clonic phase) until the muscles finally relax, and the patient is left with a disturbance of consciousness. As this is a serious event, it is seen as a major hindrance on daily life. While the seizure generally only lasts a few minutes, the patient will often feel confused, groggy or drowsy for a short period of time before returning to normal.

6. About the Pharmaceutical and Medical Devices Agency's Prior Assessment Consultation System

The prior assessment consultation system is conducted at the development stage before new drug application submission based on available quality, non-clinical and clinical data. By identifying and resolving any potential issues prior to submission, the aim is to shorten application review time as a result.

[1] French JA, et al. "Adjunctive Perampanel for Treatment of Drug-Resistant Primary Generalized Tonic-Clonic Seizures in Patients with Idiopathic Generalized Epilepsy: A Double-Blind, Randomized, Placebo-Controlled Phase III Trial." Abstract. *68th American Epilepsy Society (AES) Annual Meeting*, 2014; 2.389

[2] Hauser WA, et al. *Epilepsia*, 34(3):453-468,1993

[3] "The Epilepsies and Seizures: Hope Through Research. What are the epilepsies?" National Institute of Neurological Disorders and Stroke, accessed June 19, 2015, http://www.ninds.nih.gov/disorders/epilepsy/detail_epilepsy.htm#230253109

[4] Shorvon S, Tomson T. "Sudden unexpected death in epilepsy." *Lancet*, 2011; 378:2028-2038