No.14-52

September 19, 2014
Eisai Co., Ltd.

ARICEPT® APPROVED IN JAPAN AS TREATMENT FOR DEMENTIA WITH LEWY BODIES

WORLD'S FIRST TREATMENT FOR BOTH ALZHEIMER'S DISEASE AND DEMENTIA WITH LEWY BODIES

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today that its anti-Alzheimer's agent Aricept® (donepezil hydrochloride) has received approval for a new indication for dementia with Lewy bodies (DLB) in Japan. This marks the first time a treatment has been approved for DLB anywhere in the world.

DLB was discovered by Dr. Kenji Kosaka, Professor Emeritus of Yokohama City University. DLB is considered to be one of Japan's three major types of dementia, alongside Alzheimer's disease and vascular dementia. According to a number of reports, DLB affects between 4.3% (based on epidemiology) and 41.4% (based on autopsies) of elderly patients with dementia in Japan[1,2], with the number of patients increasing due to the aging of the population. It is pointed out that DLB is difficult to be diagnosed because the disease presents characteristic symptoms such as cognitive fluctuations, visual hallucinations and parkinsonism in addition to progressive cognitive impairment. Moreover, the development of a new treatment option has been desired by patients and medical communities, as there had been approved medication available to treat DLB.

The new indication approval was primarily based on a Phase II study (Study 431) and a Phase III study (Study 341) conducted by Eisai on patients with DLB in Japan. Also, in accordance with the conditions of approval, Eisai will work after launch to ensure that an observational study is carried out to gather data on long-term use and an additional clinical trial is performed to confirm efficacy and also promote the appropriate use of Aricept for this additional indication. The registration validity period for Aricept for this indication is 4 years.

Through this additional indication of Aricept for the treatment of DLB, Eisai will ensure and provide information of diagnosis, treatment and care of DLB and contribute to improvement the quality of life of patients. As the originator of Aricept, Eisai strives for making further contribution to the improvement of treatment and care as well as increasing public awareness towards the disease.

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[Notes to editors]

1. About Dementia with Lewy Bodies (DLB)

DLB is a degenerative form of dementia discovered in Japan that is pathologically characterized by decreased neurons in the brain and brainstem and the appearance of vast numbers of Lewy bodies. In neurochemistry, DLB is characterized by a loss of acetylcholine-producing neurons in the brain similar to that seen in patients with Alzheimer's disease. In addition to obligatory symptoms associated with progressive cognitive impairment, the disease also presents with behavioral and neuropsychiatric symptoms, motor disturbances, and dysautonomia. Of these, cognitive fluctuations, visual hallucinations and idiopathic parkinsonism have a high rate of incidence and are considered to be core symptoms of the disease[3]. In Japan, DLB constitutes one of the three major types of dementia diagnosed, alongside Alzheimer's disease and vascular dementia, affecting between 4.3% (based on epidemiology) to 41.4% (based on autopsy) of elderly patients with dementia, according to various studies[1,2].

2. Aricept Product Outline (New Information Related to Additional Indication Underlined)

1) Indications and usage

Suppression of progression of dementia symptoms in dementia of the Alzheimer's type and dementia with Lewy bodies.

2) Dosage and administration

For Aricept tablets, D tablets, fine granules, oral jelly formulation:

For the suppression of progression of dementia symptoms in dementia of the Alzheimer's type

The usual initial adult dose for oral use is 3mg of donepezil hydrochloride once daily. After 1 to 2 weeks the dose is increased to 5 mg. The dosage for patients with severe dementia of the Alzheimer's type is increased to 10 mg after dosing at 5 mg for 4 or more weeks. The dose should be reduced appropriately according to patients' symptoms.

For the suppression of progression of dementia symptoms in dementia with Lewy bodies

The usual initial adult dose for oral use is 3 mg of donepezil hydrochloride once daily. After 1 to 2 weeks the dose is increased to 5 mg. The dose is increased to 10 mg after dosing at 5 mg for 4 or more weeks. The dose can be reduced to 5 mg according to patients' symptoms.

For Aricept Dry Syrup:

For the suppression of progression of dementia symptoms in dementia of the Alzheimer's type

The usual initial adult dose for oral use is 3 mg of donepezil hydrochloride (0.3 g of dry syrup) once daily. After 1 to 2 weeks, the dose is increased to 5 mg (0.5 g of dry syrup). The dosage for patients with severe dementia of the Alzheimer's type is increased to 10 mg of donepezil hydrochloride (1.0 g of dry syrup) after dosing at 5 mg (0.5 g of dry syrup) for 4 or more weeks. The dose should be reduced appropriately according to patients' symptoms.

For the suppression of progression of dementia symptoms in dementia with Lewy bodies

The usual initial adult dose for oral use is 3 mg (0.3 g of dry syrup) of donepezil hydrochloride once daily. After 1 to 2 weeks the dose is increased to 5 mg (0.5 g of dry syrup). The dose is increased to 10 mg (1.0 g of dry syrup) after dosing at 5 mg (0.5 g of dry syrup) for 4 or more weeks. The dose can be reduced to 5 mg (0.5 g of dry syrup) according to patients' symptoms.

3) Conditions of approval

Clinical studies designed to verify the efficacy and confirm the safety of Aricept for dementia with Lewy bodies shall be conducted, and the clinical data and results analysis shall be submitted shortly after completion.

3. About the Results of Clinical Studies on Aricept in Dementia with Lewy Bodies Conducted in Japan

In an exploratory Phase II study (Study 431) of Aricept in Japanese patients with DLB, Aricept demonstrated significant improvement over placebo in core efficacy outcome measures such as cognitive function, behavioral and neuropsychiatric symptoms, and global function.

Based on the positive results of Study 431, Eisai conducted a Phase III study (Study 341) to assess the superiority of 12-week Aricept treatment over placebo in patients with DLB. The co-primary endpoints set for Study 341 were cognitive function and behavioral and neuropsychiatric symptoms. In addition, the safety and efficacy of long-term Aricept administration (52 weeks) were also investigated. Based on the results of Study 341, the expected objective of simultaneous improvement in both cognitive function as well as behavioral and neuropsychiatric symptoms was not achieved. Regarding cognitive function, statistically significant improvement was observed in the Aricept 10mg group compared to the placebo group at the final evaluation point after 12 weeks of treatment, and cognitive function was also observed to be maintained at a level higher than at baseline after 52 weeks of treatment. On the other hand, improved behavioral and neuropsychiatric symptoms were observed in all treatment groups, both Aricept and placebo, and suggested no statistically significant difference among groups at the final evaluation point after 12 weeks of treatment.

From a combined analysis of the results of Study 431 and Study 341 up to and including Week 12, the most common adverse events (AEs) observed to have occurred more frequently in the Aricept group compared to the placebo group (incidence rate greater than 3% in either treatment arm) were parkinsonism, elevated blood creatine phosphokinase, increased blood pressure, diarrhea and anorexia, and the results were consistent with the drug's safety profile as reported in patients with Alzheimer’s disease. Regarding AEs related to symptoms of parkinsonism, which occurred more often than it does in patients treated with Aricept for Alzheimer's disease, no large difference in the Aricept groups was reported, with all AEs being mild or moderate and nonserious. Furthermore, no notable difference in the incidence of AEs during the extended treatment period was found, suggesting that delayed AE onset induced by the long-term administration was unlikely to appear.

The results of both Study 431[4] and Study 341[5] have since been published in scientific papers and presented at academic conferences, respectively.

[*1] MHLW Grants System – Prevalence of dementia in urban areas and measurements for living impairment in dementia: The Report for Scientific Research, 2013

[*2] Wakisaka Y, Furuta A, Tanizaki Y, Kiyohara Y, Iida M, Iwaki T. Age-associated prevalence and risk factors of Lewy body pathology in a general population: the Hisayama study. *Acta Neuropathol* 2003; 106:374-382

[*3] McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: Third report of the DLB consortium. *Neurology* 2005; 65:1863-72.

[*4] Mori E, Ikeda M, Kosaka K. Donepezil for dementia with Lewy bodies: a randomized, placebo-controlled trial. *Ann Neurol* 2012; 72: 41-52.

[*5] Ikeda M, Mori E, Kosaka K. A clinical Phase III study of Donepezil in dementia with Lewy bodies (preliminary report): observations from a study integrating a placebo-controlled, double-blind trial and long-term administration. *The 29th Annual Meeting of the Japanese Psychogeriatric Society* 2014