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Eisai Co., Ltd.

EISAI SUBMITS APPLICATION TO EXPAND INDICATION OF ANTI-ALZHEIMER'S AGENT ARICEPT® AS TREATMENT FOR DEMENTIA WITH LEWY BODIES IN JAPAN

Eisai Co., Ltd. (Headquarters: Tokyo, President & CEO: Haruo Naito, "Eisai") announced today that it has filed an application for the anti-Alzheimer's agent Aricept® (donepezil hydrochloride, "donepezil") in Japan, requesting a new indication expansion to use the agent in the treatment of dementia with Lewy bodies (DLB).

DLB is considered to be one of Japan's three major types of dementia, alongside Alzheimer's disease and vascular dementia. In addition to progressive cognitive impairment, the disease presents with features of parkinsonism as well as visual hallucinations and other characteristic neuropsychiatric symptoms. No approved treatment for DLB currently exists, although in Japan the use of acetylcholinesterase inhibitors is recommended in the treatment of the disease according to major consensus guidelines.

Based on a preceding Phase II study (Study 431) of donepezil in Japanese patients with DLB, in which donepezil demonstrated significant improvement over placebo in core efficacy outcome measures such as cognitive function, behavioral and neuropsychiatric symptoms, and global function, Eisai conducted a Phase III study (Study 341) to assess the superiority of 12-week donepezil 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 donepezil administration (52 weeks) were also investigated. The results of Study 341 noted significant improvement in cognitive function in the donepezil groups 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. Improved behavioral and neuropsychiatric symptoms were observed in all treatment groups, both donepezil and placebo, and suggested no significant difference among groups at the final evaluation point after 12 weeks of treatment. Furthermore, adverse events (AEs) in both studies were consistent with the known safety profile of donepezil and no new or unexpected AEs occurred.

With more than 200,000 patients estimated to be living with the disease in Japan and this number expected to rise due to a rapidly aging population, the need for new DLB treatments in a clinical setting is increasing. As the originator of Aricept, Eisai is looking at the realities faced by patients with dementia in Japan and is working to further contribute to improving their quality of life (QOL) as well as the QOL of their families and caregivers.

[Please refer to the following notes for further information on DLB and the clinical study results.]

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[Notes to editors]

1. About Dementia with Lewy Bodies (DLB)

DLB is a degenerative form of dementia 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, although the extent of this loss is reportedly greater in patients with DLB. 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. In Japan, DLB constitutes one of the three major types of dementia, alongside Alzheimer's disease and vascular dementia. According to reports on DLB in the country, including a report published by a Ministry of Health, Labour and Welfare-affiliated research group, Eisai estimates that there may be as many as 200,000 patients living with DLB in Japan. Furthermore, the disease is believed to account for 10% to 20% of all dementia cases in old age in the country and there may be many more Japanese patients with DLB who have yet to be accurately diagnosed. In major consensus guidelines in Japan, the use of acetylcholinesterase inhibitors is recommended in the treatment of impaired cognitive function and behavioral and neuropsychiatric symptoms associated with DLB.

2. About the Results of the Clinical Studies Conducted in Japan

The Phase II study conducted in Japan (Study 431) was a placebo-controlled, double-blind comparative study that assessed the efficacy and safety of donepezil hydrochloride ("donepezil") administered for 12 weeks in 139 patients with dementia with Lewy bodies (DLB). In addition to assessments of cognitive function (Mini-Mental State Examination, MMSE) and global function (Clinician's Interview-Based Impression of Change-plus Caregiver Input, CIBIC-plus), the study also evaluated improvement in behavioral and neuropsychiatric symptoms that appear frequently in patients with DLB (Neuropsychiatric Inventory, NPI). Mean changes from baseline in MMSE scores at the final evaluation point were -0.4 points in the placebo group, 1.6 points in the 3 mg group, 3.4 points in the 5 mg group and 2.0 points in the 10 mg group, with statistically significant improvement observed in each donepezil group compared to the placebo group. In addition, CIBIC-plus improvement rates (those with "minimal improvement" status or better) at the final evaluation point were 33.3% in the placebo group, 68.8% in the 3 mg group, 71.0% in the 5 mg group and 64.3% in the 10 mg group, showing statistically significant improvement in each donepezil group compared to the placebo group. For behavioral and neuropsychiatric symptoms (Neuropsychiatric Inventory-10, NPI-10), mean changes from baseline in scores at the final evaluation point were 0.3 points in the placebo group, -3.9 points in the 3 mg group, -5.5 points in the 5 mg group and -8.0 points in the 10 mg group, recording statistically significant improvement in the 10 mg group compared to the placebo group. Eisai subsequently conducted Study 432 (Phase II, open-label extension study in Japan of long-term donepezil treatment) to investigate safety and efficacy. The results showed that improvement in cognitive function and behavioral and neuropsychiatric symptoms was maintained for 52 weeks of donepezil treatment. The results of both Study 431 and Study 432 have since been published.^{*1,*2}

Furthermore, a Phase III clinical study (Study 341) was conducted in Japan in 142 patients with DLB after receiving these results, combining a placebo-controlled, double-blind comparative study (12 weeks) with an open-label extension study of long-term donepezil treatment (combined duration of 52 weeks). The co-primary endpoints set for Study 341 were changes in cognitive function (MMSE) and behavioral and neuropsychiatric symptoms (Neuropsychiatric Inventory-2, NPI-2; assesses changes in visual hallucinations and cognitive changes) at the final evaluation point after 12 weeks. The results for mean changes from baseline in the MMSE scores were 0.6 points in

the placebo group, 1.4 points in the 5 mg group and 2.2 points in the 10 mg group, with statistically significant improvement observed in the 10 mg group compared to the placebo group. Meanwhile, mean changes from baseline in the NPI-2 scores at the final evaluation point were -2.1 points in the placebo group, -1.8 points in the 5 mg group and -2.8 points in the 10 mg group, with improvement reported in all groups, both donepezil and placebo, and no statistically significant difference among groups. In the extended study, improved cognitive function in patients at 12 weeks was observed to have been maintained for 52 weeks also. The results of Study 341 are planned to be published in more detail as presentations at academic conferences and in academic journals in future.

Incidence rates of adverse events (AEs), which were calculated based on a combined analysis of the results of Study 431 and Study 341 up to and including Week 12, were 68.8% in the placebo group, 68.6% in the 3 mg group, 71.3% in the 5 mg group, and 76.7% in the 10 mg group. The incidence rates of severe-but-nonserious AEs were 6.3%, 2.9%, 5.0%, and 1.2%, respectively, with the majority of these AEs reported as mild or moderate. The incidence rates of side effects were 32.5%, 45.7%, 35.0%, and 34.5%, respectively. Among the relatively more common AEs, of those side effects observed to have occurred more frequently in the donepezil groups compared to the placebo group were parkinsonism, elevated blood creatine phosphokinase, increased blood pressure, diarrhea and anorexia, although there was no significant difference among the groups and the results were consistent with the drug's safety profile as reported in patients with Alzheimer's disease. The incidence rates of AEs related to symptoms of parkinsonism, which occurred more often than it does in patients treated with donepezil for Alzheimer's disease, were 3.8% in the placebo group, 8.6% in the 3 mg group, 7.5% in the 5 mg group, and 5.8% in the 10 mg group, and no large difference in the donepezil groups was reported, with all AEs being mild or moderate and nonserious. Furthermore, in Study 432 and the Study 341 extension study, no notable difference in the incidence of AEs by onset time from start of treatment was found, suggesting that delayed AE onset induced by the long-term administration was unlikely to appear.

*¹Mori E, Ikeda M, Kosaka K. Donepezil for dementia with Lewy bodies: a randomized, placebo-controlled trial. *Ann Neurol* 2012; 72: 41-52.

*²Ikeda M, Mori E, Kosaka K, Iseki E, Hashimoto M, Matsukawa N, et al. Long-term safety and efficacy of donepezil in patients with dementia with Lewy bodies: Results from a 52-week, open-label, multi-center extension study. *Dement Geriatr Cogn Disord*. 2013; 36: 229-41.