No.24-08

January 26, 2024
Eisai Co., Ltd.

EISAI SUBMITS NEW DRUG APPLICATION FOR MECOBALAMIN ULTRAHIGH-DOSE FORMULATION IN JAPAN FOR THE INDICATION OF AMYOTROPHIC LATERAL SCLEROSIS

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today that it has submitted a New Drug Application (NDA) for ultrahigh-dose mecobalamin (development code: E0302) for the indication of amyotrophic lateral sclerosis (ALS) to the Pharmaceuticals and Medical Devices Agency (PDMA) in Japan. In May 2022, ultrahigh-dose mecobalamin received orphan drug designation by the Ministry of Health, Labour and Welfare (MHLW).

This application is based on the results of JETALS (The Japan Early-Stage Trial of Ultrahigh-Dose Methylcobalamin for ALS), a Phase III trial to evaluate efficacy and safety of ultrahigh-dose methylcobalamin (mecobalamin) in early onset ALS patients, that was conducted as an investigator-initiated trial by a research team with Extraordinary Professor Ryuji Kaji (Principal Investigator), Tokushima University, and Professor Yuishin Izumi (Coordinating Investigator), the Department of Neurology, Tokushima University Graduate School of Biomedical Sciences, and Professor Satoshi Kuwabara (Coordinating Investigator), the Department of Neurology, Chiba University Graduate School of Medicine. The results of JETALS were published in the peer-reviewed journal *JAMA Neurology*.

ALS is an intractable, progressive, neurodegenerative disease that results in severe muscle atrophy and weakness in the muscles due to motor neuron dysfunction. As the main cause of death is respiratory failure due to paralysis of the respiratory muscles, without the use of an artificial respirator, death occurs within approximately 3 to 6 years from the onset of the disease. The number of patients in Japan is estimated to be approximately 10,000. Currently, there is no curative treatment established for ALS, and since there are only limited number of medicines approved in Japan and abroad, this is a disease with significant unmet medical needs.

Eisai considers neurology a therapeutic area of focus. As a *human healthcare* company, Eisai is committed to fulfill unmet medical needs in neurology and further its contribution to improving the benefit of patients and the people in the daily living domain.

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[Notes to editors]

1. About Mecobalamin

Mecobalamin (generic name, development code: E0302) is approved and marketed as Methycobal®, a 500 μg injection of mecobalamin indicated for the treatment of peripheral neuropathies and megaloblastic anemia caused by vitamin B12 deficiency. Methycobal is also approved as a tablet formulation (250μg and 500 μg) as well as a fine granule formulation (0.1%) indicated for the treatment of peripheral neuropathies. While the mechanism of action of mecobalamin in amyotrophic lateral sclerosis (ALS) is not known, it has been suggested in non-clinical research that mecobalamin may have efficacy through a neuroprotective effect and regeneration of nerve axons. Since the 1990s, clinical research has been carried out on ultrahigh-dose mecobalamin in ALS by a study group on neurodegenerative disease, funded through the Ministry of Health, Labour and Welfare's Specified Disease Treatment Research Program. Short- and long-term trials of intramuscular injection of mecobalamin at 25 mg and 50 mg per day, which is respectively 50 and 100 times the approved dosage of Methycobal, suggested that ultrahigh-dose mecobalamin could have a clinical effect in ALS. Therefore, Eisai had conducted the Phase II/III clinical trial (Study 761) since 2006 and submitted a new drug application for ultrahigh-dose mecobalamin as treatment for ALS in May 2015 but withdrew the application in March 2016 after the Pharmaceuticals and Medical Devices Agency (PMDA) indicated that additional clinical trials were necessary.

Following favorable clinical trial results in JETALS, Eisai prepared to file a new drug application for ALS in Japan.