No.24-69

September 24, 2024
Eisai Co., Ltd.

ROZEBALAMIN® FOR INJECTION 25 MG (MECOBALAMIN) APPROVED IN JAPAN FOR AMYOTROPHIC LATERAL SCLEROSIS

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today that it has obtained manufacturing and marketing authorization approval for amyotrophic lateral sclerosis (ALS) treatment "Rozebalamin® for Injection 25 mg" (mecobalamin) in Japan as a treatment for slowing progression of functional impairment in amyotrophic lateral sclerosis. In May 2022, it received orphan drug designation, and a new drug application was submitted in January 2024, leading to this approval.

This approval is based on the results of JETALS (The Japan Early-Stage Trial of Ultrahigh-Dose Methylcobalamin for ALS), multicenter, placebo-controlled, double-blind, randomized Phase III clinical trial in 130 patients with ALS, 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.
In JETALS, the mecobalamin 50mg group showed a statistically significant slowing of progression compared to the placebo group in the change in total score from the end of the observation period to week 16 of the treatment period in the primary endpoint, the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) (slowing decline by approximately 43%, p=0.01).[1] The adverse drug reaction incidence rates were 1.6% in the placebo group and 7.7% in the mecobalamin 50 mg group. Adverse reactions observed in the mecobalamin 50 mg group included constipation, injection site pain, fever, electrocardiogram QT prolongation and rash, each occurring in 1.5% of patients.[2]

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 2 to 5 years from the onset of the disease.[3] The number of patients in Japan is estimated to be approximately 10,000.[3] 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 further addressing the diverse needs of, and increasing the benefits of, patients and their families by providing Rozebalamin as a new treatment option for ALS patients.

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[Notes to editors]

1. Product Outline

1) Product name

Rozebalamin® for Injection 25 mg

2) Generic name

Mecobalamin

3) Indication for use

Slowing progression of functional impairment in amyotrophic lateral sclerosis

4) Dosage and administration

The usual dose of mecobalamin in adults is 50 mg a day, twice a week, injected intramuscularly.

2. About Rozebalamin (generic name: mecobalamin, development code: E0302)

Mecobalamin 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 (250 μg 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 against 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, and Eisai then conducted the Phase II/III clinical trial (Study 761) from 2006. Eisai 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.

After obtaining favorable results in the investigator-initiated Phase III trial JETALS, and following consultation with Tokushima University, Eisai submitted a new drug application for the treatment of ALS in Japan in January 2024, leading to this approval.

3. About Japan Early-stage Trial of Ultrahigh-Dose Methylcobalamin for ALS (JETALS)

The Japan Early-stage Trial of Ultrahigh-Dose Methylcobalamin for ALS (JETALS) is an investigator-initiated study conducted as a multicenter, placebo-controlled, double-blind, randomized Phase III clinical trial to verify the efficacy and safety of high-dose methylcobalamin (mecobalamin) in patients with amyotrophic lateral sclerosis (ALS).[1]

Mecobalamin 50 mg or placebo was administered intramuscularly twice weekly for 16 weeks to 130 ALS patients who had suffered from ALS for less than one year, were classified as “definite”, “probable”, or “probable-laboratory supported” according to the Updated Awaji Criteria, had an ALS severity rating of grade 1 or 2, had a decrease of 1 or 2 points in the total score on the Revised ALS Functional Rating Scale-Revised (ALSFRS-R) 12 weeks prior to administration, and had a forced vital capacity (%FVC) of more than 60%.[2]

The primary endpoint was the change in ALSFRS-R total score from the end of the observation period to week 16 of the treatment period. The change was -2.7 [95% confidence interval (CI): -3.9, -1.5] in the mecobalamin

50 mg group and -4.6 [95% CI: -5.8, -3.4] in the placebo group, with a difference in change of 2.0 (95% CI: 0.4, 3.5; p=0.012), verifying the superiority of mecobalamin 50 mg over placebo.[2] The adverse drug reaction incidence rate was 1.6% (1/64 cases) in the placebo group and 7.7% (5/65 cases) in the mecobalamin 50 mg group. Adverse drug reactions observed in the mecobalamin 50 mg group were constipation, injection site pain, fever, electrocardiogram QT prolongation, and rash, occurring in 1.5% (1/65 cases) each.[2]

1. Oki R, et al. Efficacy and safety of ultrahigh-dose methylcobalamin in early-stage amyotrophic lateral sclerosis a randomized clinical trial. *JAMA Neurol.* 2022;79(6):575-583.
2. Information stated in the package insert.
3. Japan Intractable Diseases Information Center, Amyotrophic lateral sclerosis (ALS), Designated intractable disease (2). https://www.nanbyou.or.jp/entry/52. Last accessed: September 2024. (Japanese only)