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Eisai Co., Ltd.

Update on the Cost-Effectiveness Evaluation of LEQEMBI® by the Central Social Insurance Medical Council of Japan's Ministry of Health, Labour and Welfare

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today that the expert committee of the Central Social Insurance Medical Council (Chuikyo), part of Japan's Ministry of Health, Labour and Welfare (MHLW) has published the conclusion of the cost-effectiveness evaluation for humanized anti-soluble aggregated amyloid beta (Aβ) monoclonal antibody LEQEMBI® Intravenous Infusion (Lecanemab). The analysis is based on the C2H/ERG (Center for Outcomes Research and Economic Evaluation for Health/ External Research Group) Analysis results*1.

The the cost-effectiveness evaluation was conducted in accordance with the special framework for evaluating the cost-effectiveness of LEQEMBI (LEQEMBI Special Framework*2), which was approved by the Central Social Insurance Medical Council (Chuikyo) in December 2023. In this cost-effectiveness evaluation process, the Corporate Analysis results submitted by Eisai were reviewed and reanalyzed. Both the "Corporate An analysis results" and the "C2H/ERG Analysis review and reanalysis results (C2H/ERG Analysis results)" were then deliberated by the expert committee on Cost-Effectiveness Evaluation of Chuikyo.

In the cost-effectiveness evaluation of LEQEMBI, analysis from the standpoint of public healthcare and long-term care—which included public caregiving—was, for the first time in Japan, subject to deliberation. In the C2H/ERG Analysis, the treatment of public caregiving costs was also taken into account. However, the Corporate and Public Analyses had different structures for the analytical models and differences in methods used to estimate LEQEMBI's effectiveness and calculate caregiver QOL. The differences between the two analyses are shown below.

Corporate vs. C2H/ERG Analysis: Key Distinctions in Base-Case Scenarios

	Corporate Analysis	C2H/ERG Analysis
Analytical Model	・ A Markov model commonly used in cost-effectiveness evaluations ・ A standard model that can estimate the long-term progression of Alzheimer's disease pathology ・ Consideration of continued administration of LEQEMBI beyond 18 months	・ Model developed by Chuikyo ・ LEQEMBI treatment period limited to 18 months in base case ・ Progression slowing effect of LEQEMBI after 18 months administration applied exclusively to the MCI stage
Effectiveness	・ Evaluate the effect of slowing long-term disease progression (Hazard Ratio = 0.704)	・ LEQEMBI's effectiveness is define as a 5.3 month slowing of disease

	・ Effect continues even after discontinuation of LEQEMBI	progression after 18 months of treatment ・ LEQEMBI loses its effectiveness immediately after discontinuation
Caregiver QOL	・ Additive approach: Applying caregiver QOL directly	・ Method uniquely developed by C2H/ERG Analysis that reflects only the improvement effect on caregiver burden during MCI stage

Analysis Models

Cost-effectiveness evaluations use simulation models to estimate the effects of treatments. AD is characterized by a long-term progression of pathology and disease stages over several years or even decades. Therefore, to accurately assess the impact of treatment, long-term projections are essential.

In conducting our corporate analysis, we built and analyzed a cost-effectiveness evaluation model for LEQEMBI (Corporate Analysis model) based on the Markov model, a standard framework commonly used for long-term disease progression forecasting in Alzheimer's disease (AD) and other conditions. Eisai has presented three-year efficacy data from the Clarity AD Open Label Extension (OLE) to the scientific community and incorporated this data into the Corporate Analysis model for long-term projections. In cost-effectiveness evaluations, an important factor is how accurately the model reproduces actual clinical conditions.[1,2] We validated the Corporate Analysis model in accordance with the recommendations of the International Society for Health Economics and Outcomes Research (ISPOR).[1] In addition, "The Cost-Effectiveness Evaluation Analysis Guidelines by the Central Social Insurance Medical Council (Chuikyo)" require validation of the models used for cost-effectiveness evaluations.[2]

By comparison, the C2H/ERG Analysis retained the long-term projections for the standard treatment group derived from our Corporate Analysis model. However, it did not apply the long-term projections from the Corporate Analysis model to the LEQEMBI treatment group. Instead, the C2H/ERG Analysis model limited LEQEMBI administration to 18 months and extrapolated the 5.3-month progression slowing period observed at the 18-month treatment milestone in the Clarity AD study directly onto the mild cognitive impairment (MCI) phase of the standard treatment group from the Corporate Analysis. The C2H/ERG Analysis model also assumed identical durations for the mild and moderate AD stages between the LEQEMBI and standard treatment groups. Based on that assumption, the C2H/ERG Analysis used a unique method to shorten the extension of overall survival period to less than 5.3 months.

Thus, in the C2H/ERG Analysis model, the administration period for LEQEMBI is limited to 18 months, and its long-term efficacy is not reflected. Moreover, the characteristics and actual conditions of AD are not taken into consideration. Therefore, the simulation model is considered to be insufficiently validated as a cost-effectiveness evaluation.

Effectiveness

In the Corporate Analysis, disease progression forecasting was conducted based on the results of the Clarity AD study, utilizing actual clinical data whenever possible, including information on age and gender

distribution. In addition, to make long-term projections taking into account continued administration beyond 18 months, the hazard ratio of 0.704 as long-term efficacy data obtained during the OLE period following the Clarity AD study was used as a measure of the risk of progression to the next disease stage. Since the results of the OLE phase showed that the clinical assessment measure CDR-SB showed a widening gap between the LEQEMBI treatment group and the natural disease progression observed in the comparator group from Alzheimer's Disease Neuroimaging Initiative (ADNI)*3 as was widening, the assumption that efficacy will continue as long as administration is continued is used in the Corporate Analysis.

Regarding the efficacy of LEQEMBI following treatment discontinuation, there is currently no appropriate evidence available. Therefore, we initially assumed that the hazard ratio prior to discontinuation would remain unchanged. However, to deepen discussions on cost-effectiveness evaluation, we also proposed an alternative assumption—a "waning efficacy scenario" in which efficacy gradually declines over a certain period—to the Cost-Effectiveness Evaluation Expert Committee of Chuikyo. In the follow-up evaluation conducted three months after the completion of 18 months of treatment in the Phase II clinical trial (Study 201), it was shown that suppression of clinical deterioration, including CDR-SB scores, persisted compared to the placebo group. Eisai convened an advisory board composed of several Japanese clinical experts with long-term administration experience from clinical trials. The board expressed the view that the effect does not disappear immediately after cessation, although no evidence has been obtained regarding the magnitude or duration of LEQEMBI's effect after treatment discontinuation. This opinion was also presented during the deliberation process of the cost-effectiveness evaluation.

In contrast, in base case, the C2H/ERG Analysis limits the treatment duration to 18 months and defines LEQEMBI's efficacy solely based on the 5.3-month slowing progression effect observed at the 18-month treatment. As a result, long-term projections beyond 18 months cannot be appropriately conducted.
In the C2H/ERG Analysis, although it is acknowledged that efficacy does not immediately disappear after discontinuation of LEQEMBI, the model assumes that efficacy ceases immediately due to the difficulty in quantitatively measuring post-discontinuation effects.

In cost-effectiveness evaluations, it is essential to use a model that enables appropriate assessment based on scientifically demonstrated long-term efficacy data and allows for long-term projections that reflect such efficacy. However, we believe that the C2H/ERG Analysis ultimately did not take these factors into account, resulting in an underestimation of the long-term effectiveness of LEQEMBI.

Caregiver Quality of Life

In the Corporate Analysis, we applied an additive approach, a methodology that reflects caregiver quality of life (QOL) to cost effective evaluation, using the actual caregiver QOL data collected in the Clarity AD study. Unlike the traditional Decrement approach—which subtracts the reduction in caregiver QOL caused by caregiving burden from the patient's QOL—or methods that assess only the caregiver's burden, the Additive approach recognizes the value of time spent together with the patient as part of the caregiver's

own QOL. This aligns with the goals of “The Basic Act on Dementia to Promote an Inclusive Society”, which aims to enable people with dementia and their families to live in their own way in the community. The Additive approach is expected to undergo further academic validation as a method for appropriately evaluating caregiver QOL.

In contrast, the C2H/ERG Analysis focuses not on the caregiver’s QOL but solely on caregiving burden, calculating changes in caregiver QOL across disease stages (MCI, mild AD, moderate AD, and severe AD) based on differences from the previous stage. In this model, caregiver QOL during the severe AD stage is set to zero, reflecting the high burden. Moreover, as noted above, the C2H/ERG Analysis model assumes identical durations for the mild and moderate AD stages between the LEQEMBI and standard treatment groups. As a result, no difference in caregiver QALY*4 appeared between the standard and LEQEMBI groups during the mild, moderate, or severe AD stages. Consequently, only the caregiver QOL improvement during the MCI stage—which involves a lesser burden—is reflected in the cost-effectiveness evaluation, leading to an underestimation of caregiver QOL in LEQEMBI group.

In Japan’s cost-effectiveness evaluation system, this is the first case where caregiver QOL has been assessed. There remains concern that future evaluations within the unique C2H/ERG Analysis framework may continue to undervalue caregiver QOL.

ICER Based on Corporate Analysis

The result of Eisai’s corporate analysis regarding the cost-effectiveness of LEQEMBI showed that the Incremental Cost-Effectiveness Ratio (ICER)*5 for the MCI (Mild Cognitive Impairment) cohort, where treatment commences from the MCI stage, was ¥7,297,814 / QALY (Quality-Adjusted Life Year)*4 from the perspective of public healthcare and long-term care payers’ and ¥8,034,845 / QALY from the perspective of public healthcare payers’. Furthermore, for the mild AD cohort, where treatment commences from the mild AD stage, the ICERs were ¥6,055,342 / QALY from the perspective of public healthcare and long-term care payers’ and ¥6,647,097 / QALY from the perspective of public healthcare payers, respectively.

Under the LEQEMBI special framework, the reference threshold for cost-effectiveness evaluation is set at 5 million yen per QALY. However, in our corporate analysis, when applying a threshold of 7.5 million yen per QALY, which is used for diseases requiring special consideration, the public healthcare and long-term care perspective yields a value of 7,297,814 yen per QALY, which is nearly equivalent to the current drug price. In Japan’s cost-effectiveness evaluation system, a threshold of 7.5 million yen per QALY is applied to diseases requiring special consideration, such as rare diseases, pediatric conditions, and cancer therapies. We believe that AD also warrants such consideration due to its severity and disease burden.*6

Meanwhile, the Institute for Clinical and Economic Review in the United States has presented benchmark prices for LEQEMBI based on four willingness-to-pay (WTP) thresholds: $50,000, $100,000, $150,000, and $200,000 per QALY. Japan’s threshold of 5 million yen per QALY falls below the lowest of these benchmarks. Additionally, the World Health Organization (WHO) recommends using 1 to 3 times GDP per capita as a general guideline for cost-effectiveness thresholds. While this allows for a broad range,

it also highlights the challenge that evaluation outcomes can be heavily influenced by the chosen threshold.

This cost-effectiveness evaluation is an evaluation of the price based on the LEQEMBI Special Framework and does not affect the effectiveness or efficacy of LEQEMBI. Eisai has a mission to communicate the fair value of LEQEMBI to patients receiving the drug, their families, and those who wish to receive LEQEMBI. Eisai will continue to disseminate the true value of LEQEMBI based on actual clinical practice through academic publications etc. and will continue to seek a fair evaluation of the value that LEQEMBI brings.

Eisai serves as the lead of LEQEMBI development and regulatory submissions globally with both Eisai and Biogen Inc. (U.S.) co-commercializing and co-promoting the product and Eisai having final decision-making authority.

*1 General Assembly of the Central Social Insurance Medical Council (https://www.mhlw.go.jp/stf/newpage_59377.html) (only in Japanese)

*2 Rather than using the conventional method of adjusting prices based on the Usefulness Premium, this is a special pricing framework that calculates the difference from the price at which the Incremental Cost-Effectiveness Ratio (ICER) reaches 5 million yen per QALY and adjusts the price accordingly. (https://www.mhlw.go.jp/content/001179940.pdf)

*3 The Alzheimer's Disease Neuroimaging Initiative (ADNI) is a clinical research project launched in 2005 to develop methods for predicting the onset of AD and evaluating treatment efficacy. The ADNI observational cohort represents a population comparable to participants in the Clarity AD trial. ADNI participants with similar backgrounds to those in the Clarity AD trial exhibited disease progression comparable to the placebo group in the 18-month core phase of the Clarity AD study.

*4 Quality-Adjusted Life Year (QALY) is a measure of the value of health outcomes, calculated by multiplying a QOL score by Life Year.

*5 Incremental Cost-Effectiveness Ratio (ICER): An evaluation metric in cost-effectiveness analysis that represents the ratio of the incremental cost to the incremental effectiveness (e.g., additional health benefit gained).

*6 AD is a progressive and debilitating condition, placing a significant burden on QOL, daily function, caregivers, and the healthcare system. As a result, setting a higher threshold value (WTP) than standard is likely to be allowed when evaluating the value of treatment. Research by Lakdawalla et al. (2020)3 suggests weighting reference values by disease severity, where the threshold for severe AD could be up to five times higher than that for a standard condition such as peptic ulcer.

References

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