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Eisai Co., Ltd.

ANTICANCER AGENT "TAZVERIK® TABLETS 200mg" (TAZEMETOSTAT HYDROBROMIDE) LAUNCHED IN JAPAN FOR *EZH2* GENE MUTATION-POSITIVE FOLLICULAR LYMPHOMA

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today that it has launched the anticancer agent EZH2 inhibitor "Tazverik® Tablets 200 mg" (tazemetostat hydrobromide), in Japan with the indication of relapsed or refractory *EZH2* gene mutation-positive follicular lymphoma (only when standard treatment is not applicable). Eisai obtained the manufacturing and marketing approval of "Tazverik" on June 23, 2021. "Tazverik" was included to Japan's National Health Insurance Drug Price List on August 12, 2021.

Created by utilizing Epizyme, Inc. (Headquarters: Massachusetts, United States)'s proprietary product platform, "Tazverik" is a first-in-class small molecule inhibitor of the epigenetic enzyme EZH2. It is one of the histone methyltransferases in the epigenetics-related protein group, and is thought to regulate the expression of cancer-related genes and suppress the growth of cancer cells by specifically targeting EZH2, which contributes to the cancer growth process.[1] Eisai is responsible for the development and commercialization of this agent in Japan, while Epizyme, Inc. is responsible for all regions outside of Japan. The approval of "Tazverik" in Japan is based on data including results from Study 206,[2] which is a multicenter, open-label, single-arm Phase II clinical study conducted in Japan by Eisai, and other clinical studies[3] conducted by Epizyme, Inc. outside of Japan.

Follicular lymphoma is a low-grade B-cell lymphoma that accounts for 10-20% of non-Hodgkin's lymphomas. Follicular lymphoma is generally indolent and sensitive to chemotherapy. However, development of a new treatment strategy is required for follicular lymphoma, which still remains difficult to cure as recurrence often occurs repeatedly. 7-27% of follicular lymphomas are reported to have gain-of-function mutations in the *EZH2* gene,[4,5] and it is estimated that there are approximately 600 to 2,400 patients with follicular lymphoma with *EZH2* gene mutations in Japan. A companion diagnostic test for *EZH2* gene mutations, "cobas® EZH2 Mutation Test" by Roche Diagnostics K.K. (Headquarters: Tokyo) was approved in May 2021.

For the production of this drug, Eisai is applying "Continuous Manufacturing", an innovative pharmaceutical production technology, which was successfully developed at the Kawashima Industrial Park (Gifu

Prefecture). It is the first time for Eisai to obtain a manufacturing license for Continuous Manufacturing. Continuous Manufacturing is a production method in which raw materials are continuously fed into the manufacturing process and finished products are continuously taken out. It is an advanced production technology that combines manufacturing automation and real-time quality monitoring technology. The space-saving, energy-saving system achieves high production efficiency that leads to a reduction in environmental impact, and contributes to improved quality and stable supply of pharmaceuticals.

Eisai will deliver "Tazverik" as a new treatment option for *EZH2* gene mutation-positive follicular lymphoma, and will appropriately conduct a post-marketing special use results survey (all-case surveillance) in accordance with an approval condition imposed by the Ministry of Health, Labour and Welfare (MHLW) and promote the proper use of this agent. Eisai is committed to exploring the potential clinical benefits of "Tazverik" for cancer treatment, as it seeks to contribute to addressing the diversified needs of, and increasing the benefits provided to, patients with cancer, their families and healthcare professionals.

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[Notes to editors]

1. Product Information

1) Brand name
"Tazverik® Tablets 200 mg"

2) Generic name
Tazemetostat hydrobromide

3) Indications
Relapsed or refractory *EZH2* gene mutation-positive follicular lymphoma (only when standard treatment is not applicable)

4) Dosage and Administration
The usual adult dose of tazemetostat is 800mg orally twice daily. The dose may be reduced appropriately according to the condition of the patient.

5) National Health Insurance (NHI) Drug Price
Tazverik Tablets 200 mg: ¥ 3,004.60 (per 1 tablet)

6) Packaging
Tazverik Tablets 200 mg: 56 tablets (14 tablet PTP sheet X 4)

2. About "Tazverik Tablets 200 mg" (tazemetostat hydrobromide)

"Tazverik" is a first-in-class, oral small molecule inhibitor that targets EZH2. Eisai and Epizyme, Inc. have conducted joint research and development with utilizing Epizyme, Inc.'s proprietary product platform, based on the alliance agreement concluded in March 2011 targeting EZH2 for research, development, and sales. This agent selectively inhibits EZH2 in a competitive matter with S-adenosylmethionine (a methyl group donor) to suppress methylation of H3K27. Due to the alteration in the alliance agreement between the two companies in March 2015, Eisai is responsible for development and commercialization of this agent in Japan, while Epizyme, Inc. is responsible for all regions outside Japan.

For the production of this drug, Eisai is applying Continuous Manufacturing, an innovative pharmaceutical production technology, which was successfully developed at the Kawashima Industrial Park. It is the first time for Eisai to obtain a manufacturing license for Continuous Manufacturing. Continuous Manufacturing is a production method in which raw materials are continuously fed into the manufacturing process and finished products are continuously taken out. It is an advanced production technology that combines manufacturing automation and real-time quality monitoring technology. The space-saving, energy-saving system achieves high production efficiency that leads to a reduction in

environmental impact, and contributes to improved quality and stable supply of pharmaceuticals. Eisai was one of the first to adopt Continuous Manufacturing system (CTS-MiGRA) and applied this technology to the production of this agent.

The accelerated approval was granted for this agent in January 2020 in the United States with the indication of “adults and pediatric patients aged 16 years and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection”. Also, in June of the same year, the accelerated approval was granted for this agent with the indication of “adult relapsed / refractory follicular lymphoma who had at least 2 regimens of prior treatment and whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test”, and of “adult relapsed / refractory follicular lymphoma for which there are no satisfactory alternative treatment options”.

3. About Study 206

Study 206 enrolled patients with *EZH2* gene mutation-positive, primarily follicular lymphoma, who had relapsed or were refractory. The primary endpoint of this study was objective response rate (ORR), and secondary endpoints included safety. This study achieved the primary endpoint target and exceeded a prespecified tumor response threshold with statistical significance: ORR in patients with EZH2 mutation-positive relapsed or refractory follicular lymphoma (n=17) was 76.5% (90% confidence interval (CI): 53.9-91.5) as measured by independent review. Treatment-emergent adverse events (incidence of 25% or more) observed in this study were dysgeusia (52.9%), nasopharyngitis (35.3%), lymphopenia (29.4%) and blood creatine phosphokinase increased (29.4%).

4. About epigenetics

Epigenetics is a branch of science that studies the mechanism for the acquired activation / inactivation of gene function and seeks to determine how gene function is inherited through cell division, irrespective of DNA base sequence alteration. Examples of modification that lead to the regulation of gene expression include methylation of DNA and modifications of histone (methylation, acetylation, phosphorylation, etc.).

5. About EZH2

EZH2 is one of the histone methyltransferases within a larger class of epigenetics-related proteins, and specifically catalyzes the methylation of histone H3 at lysine 27 (H3K27), thus controlling expression of various genes. It is indicated that an increase in methylation of H3K27 caused by EZH2 gain-of-function mutation, overexpression, or the dysfunction of EZH2 suppressive factors plays an important role in carcinogenesis.

[1] Sarah K. Knutson, Satoshi Kawano, Yukinori Minoshima, et al. Selective Inhibition of EZH2 by EPZ-6438 Leads to Potent Antitumor Activity in EZH2-Mutant Non-Hodgkin Lymphoma. *Molecular Cancer Therapeutics*. 2014 Apr; 13(4):842–854.

[2] Shinya Rai, et al. Phase 2 Study of Tazemetostat in Japanese patients with Relapsed or Refractory EZH2 mutation-positive B-cell Non-Hodgkin’s Lymphoma. *AACR Meet.* 2021, CT176.

[3] Franck Morschhauser, et al. Tazemetostat for patients with relapsed or refractory follicular lymphoma: an open-label, single-arm, multicentre, phase 2 trial. *The Lancet Oncology.* 2020 Nov; 21(11):1433-1442.

[4] Csaba Bödör, et al. EZH2 mutations are frequent and represent an early event in follicular lymphoma. *Blood*, 2013 Oct; 122(18), 3165-3168.

[5] Ryan D. Morin, et al. Somatic mutation of EZH2 (Y641) in Follicular and Diffuse Large B-cell Lymphomas of Germinal Center Origin. *Nature Genetics*. 2010 Feb; 42(2):181–185.