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Eisai Co., Ltd.

## **EISAI'S ANTICANCER AGENT HALAVEN<sup>®</sup> NEWLY APPROVED IN JAPAN FOR TREATMENT OF SOFT TISSUE SARCOMA**

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today that it has received approval in Japan for its in-house developed anticancer agent Halaven<sup>®</sup> (eribulin mesylate) as a treatment of patients with soft tissue sarcoma. Halaven is the first and only single agent to demonstrate an overall survival (OS) benefit in a Phase III trial in patients with advanced, recurrent or metastatic soft tissue sarcoma (liposarcoma or leiomyosarcoma). Following approval for use in the treatment of inoperable or recurrent breast cancer in Japan, this marks the second indication for which Halaven has been approved based on a statistically significant extension of OS.

In a Phase III clinical study (Study 309) in patients with locally advanced, locally recurrent or metastatic soft tissue sarcoma (liposarcoma or leiomyosarcoma) who had disease progression following standard therapies which must have included an anthracycline and at least one other additional regimen, Halaven demonstrated a statistically significant extension in the study's primary endpoint of OS over the comparator treatment dacarbazine.<sup>1</sup> The most common adverse reactions (incidence greater than or equal to 25%) in patients treated with Halaven in the study were neutropenia, fatigue, alopecia, nausea, and peripheral neuropathy, which was consistent with the known side-effect profile of Halaven. Furthermore, in a Phase II clinical study (Study 217) of Halaven in patients with advanced or recurrent soft tissue sarcoma who had received chemotherapy conducted within Japan, the results also suggested clinical efficacy for Halaven.<sup>2</sup>

Soft tissue sarcoma is a collective term for a diverse group of malignant tumors that occur throughout the soft tissues (including fat, muscle, nerves, fibrous tissues and blood vessels) in the body. According to a patient survey conducted by Japan's Ministry of Health, Labour and Welfare, there are approximately 4,000 patients with soft tissue sarcoma in Japan.

In January 2016, Halaven was approved in the United States as a treatment of patients with unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen, and applications seeking approval for use in the treatment of soft tissue sarcoma are currently under review in the EU, Switzerland, Russia, Australia, and Brazil. Halaven has been designated as an orphan drug for the treatment of soft tissue sarcoma in the United States and Japan.

Halaven is a halichondrin class microtubule dynamics inhibitor with a distinct binding profile. Recent non-clinical studies showed that Halaven is associated with increased vascular perfusion and permeability in tumor cores.<sup>3</sup> Halaven promotes the epithelial state and decreases the capacity of breast cancer cells to migrate.<sup>4</sup> Halaven is currently approved for use in the treatment of breast cancer in approximately 60 countries including Japan and countries in Europe, the Americas and Asia.

Through obtaining this additional approval, Eisai aims to enhance the clinical value of Halaven to contribute further toward addressing the diverse needs of, and increasing the benefits provided to, patients with cancer, their families, and healthcare providers.

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## [Notes to editors]

### 1. Product Outline (New Information Related to Additional Indication Underlined)

- 1) Product name  
Halaven<sup>®</sup> Injection 1 mg
- 2) Generic name  
Eribulin mesylate
- 3) Indication for use  
Inoperable or recurrent breast cancer, soft tissue sarcoma
- 4) Dosage and administration

The usual adult dose of eribulin mesylate is 1.4 mg/m<sup>2</sup> body surface area, administered intravenously as a single dose over 2 to 5 minutes, once a week. Treatment should be continued for 2 consecutive weeks, followed by a third week of drug cessation. With each cycle lasting 3 weeks, the treatment should be repeated. The dose may be reduced, depending on the condition of the individual patient.

### 2. About Halaven

Halaven is the first in the halichondrin class of microtubule dynamics inhibitors with a novel mechanism of action. Structurally Halaven is a simplified and synthetically produced version of halichondrin B, a natural product isolated from the marine sponge *Halichondria okadai*. Halaven is believed to work by inhibiting the growth phase of microtubule dynamics which prevents cell division. In addition, recent non-clinical studies showed that Halaven is associated with increased vascular perfusion and permeability in tumor cores.<sup>3</sup> Halaven promotes the epithelial state and decreases the capacity of breast cancer cells to migrate.<sup>4</sup>

Halaven was first approved in November 2010 in the United States as a treatment for patients with metastatic breast cancer who have received at least two chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting. Halaven is currently approved for use in the treatment of breast cancer in approximately 60 countries worldwide, including Japan and countries in the Europe, Americas and Asia. In Japan, Halaven has been approved to treat inoperable or recurrent breast cancer and was launched in the country in July 2011. Halaven has also been approved in countries in Europe and Asia indicated as a treatment for patients with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting, unless patients were not suitable for these treatments.

Regarding soft tissue sarcoma, Halaven was approved in the United States for the treatment of patients with unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen in January 2016, and was approved in Japan for the treatment of soft tissue sarcoma in February 2016. Applications seeking approval for use in the treatment of soft tissue sarcoma are currently under review in the EU, Switzerland, Russia, Australia, and Brazil. Furthermore, Halaven has been designated as an orphan drug for soft-tissue sarcoma in the United States and Japan.

### 3. About Soft Tissue Sarcoma

Soft tissue sarcoma is a collective term for a diverse group of malignant tumors that occur throughout the soft tissue (including fat, muscle, nerves, fibrous tissues and blood vessels) in the body. Approximately 12,000 patients in the United States and 29,000 patients in Europe are diagnosed with soft tissue sarcoma each year. According to a patient survey conducted by Japan's Ministry of Health, Labour and Welfare, there are approximately 4,000 patients with soft tissue sarcoma in Japan. As the structures where the tumors originate are diverse, there are various types of soft tissue sarcoma, and the most common types include leiomyosarcoma, liposarcoma and malignant fibrous histiocytoma. While treatment of soft tissue sarcoma is focused on curative surgery, if the degree of malignancy is high, treatment then becomes a combination of chemotherapy and radiation therapy. As outcomes are poor for patients with advanced disease, it remains a disease with significant unmet medical need.

#### 4. About Study 309<sup>1</sup>

Conducted primarily in Europe and the United States, Study 309 was a multicenter, open-label, randomized Phase III study comparing the efficacy and safety of Halaven (“eribulin”) versus dacarbazine in 452 patients (aged 18 or over) with locally advanced, locally recurrent or metastatic soft tissue sarcoma (liposarcoma or leiomyosarcoma) who had disease progression following standard therapies which must have included an anthracycline and at least one other additional regimen. Patients received either eribulin (1.4 mg/m<sup>2</sup> administered intravenously on Day 1 and Day 8) or dacarbazine (850–1200 mg/m<sup>2</sup> administered intravenously on Day 1) every 21 days until disease progression.

From the results for the study, eribulin demonstrated a statistically significant extension in the study’s primary endpoint of overall survival (OS) over the comparator treatment dacarbazine (eribulin median OS: 13.5 months vs dacarbazine median OS: 11.5 months; Hazard Ratio 0.77 [95% CI=0.62-0.95], p=0.0169). Furthermore, in the study’s secondary endpoints, there was no statistically significant difference found between eribulin and dacarbazine in either progression-free survival (PFS) (median PFS: 2.6 months in both arms) or progression-free rate at 12 weeks (PFR<sub>12wks</sub>) (eribulin PFR<sub>12wks</sub>: 33% vs dacarbazine PFR<sub>12wks</sub>: 29%).

The most common adverse reactions (incidence greater than or equal to 25%) in study patients with liposarcoma or leiomyosarcoma treated with eribulin were neutropenia, fatigue, alopecia, nausea, and peripheral neuropathy, which was consistent with the known side-effect profile of eribulin.

#### 5. About Study 217 (Results Presented at 50th Meeting of the American Society of Clinical Oncology)<sup>2</sup>

Conducted in Japan, Study 217 was an open label, multicenter, Phase II study to evaluate the efficacy and safety of eribulin in 51 previously treated subjects with advanced or recurrent soft tissue sarcoma. Patients in the study received eribulin (1.4 mg/m<sup>2</sup> administered intravenously on Day 1 and Day 8) every 21 days until disease progression, and the primary endpoint was PFR<sub>12wks</sub>.

The results of the study demonstrated efficacy for eribulin in previously treated patients with advanced soft tissue sarcoma. PFR<sub>12wks</sub> in all evaluated groups of soft tissue sarcoma was 51.0%. Furthermore, the PFR<sub>12wks</sub> in patients with liposarcoma or leiomyosarcoma (35 patients) and in patients with other types of soft tissue sarcoma (16 patients) were 60.0% and 31.3%, respectively.

The most common treatment emergent adverse events of Grade 3 or higher (Common Terminology Criteria for Adverse Events) were neutropenia (86.3%), white blood cell decrease (74.5%), lymphocyte decrease (31.4%), anemia (11.8%) and febrile neutropenia (7.8%).

<sup>1</sup> Schöffski P et al. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. *The Lancet*. 2016.

<sup>2</sup> Naito Y, et al. Phase II study of eribulin mesylate in patients with advanced soft tissue sarcoma (STS). *ASCO Meet. Abstr.* 2014, 10667

<sup>3</sup> Funahashi Y et al. Eribulin mesylate reduces tumor microenvironment abnormality by vascular remodeling in preclinical human breast cancer models. *Cancer Sci.*, 2014; 105, 1334-1342

<sup>4</sup> Yoshida T et al. Eribulin mesilate suppresses experimental metastasis of breast cancer cells by reversing phenotype from epithelial-mesenchymal transition (EMT) to mesenchymal-epithelial transition (MET) states. *Br J Cancer*, 2014; 110, 1497-1505