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Eisai Co., Ltd.

U.S. FDA APPROVES EISAI'S ANTICANCER AGENT HALAVEN® FOR THE TREATMENT OF ADVANCED LIPOSARCOMA

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today that its U.S. subsidiary Eisai Inc. has received approval from the U.S. Food and Drug Administration (FDA) of its in-house developed anticancer agent Halaven® (eribulin mesylate) for the treatment of patients with unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen. Halaven is the first and only single agent to demonstrate an overall survival (OS) benefit in a Phase III trial in patients with advanced or recurrent and metastatic soft tissue sarcoma (leiomyosarcoma or liposarcoma). Following approval for use in the treatment of metastatic breast cancer in the United States, this marks the second indication for which Halaven has been approved by the FDA based on a statistically significant extension of OS.

This approval was based on the results from a multicenter, open-label, randomized Phase III study (Study 309) comparing the efficacy and safety of Halaven versus dacarbazine in 452 patients (aged 18 or over) with locally advanced or recurrent and 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 (Halaven median OS: 13.5 months vs dacarbazine median OS: 11.5 months; Hazard Ratio (HR) 0.768 [95% CI=0.618-0.954], p=0.017).[1]
For patients with liposarcoma, Halaven demonstrated a significant improvement in OS over dacarbazine (Halaven, n=71, median OS: 15.6 months vs dacarbazine, n=72, median OS: 8.4 months; HR 0.51 [95% CI=0.35-0.75]).[2] Additionally, in the study's secondary endpoint of progression-free survival (PFS), patients treated with Halaven experienced an improvement in PFS over dacarbazine (Halaven median PFS: 2.9 months vs dacarbazine median PFS: 1.7 months; HR 0.52 [95% CI=0.35-0.78]).[2]

The most common adverse reactions (incidence greater than or equal to 25%) in study patients with liposarcoma and leiomyosarcoma treated with Halaven were fatigue, nausea, alopecia, constipation, peripheral neuropathy, abdominal pain and pyrexia, which was consistent with the known side-effect profile of Halaven.[2] The most common (incidence greater than or equal to 5%) Grade 3-4 laboratory abnormalities reported in patients receiving Halaven were neutropenia, hypokalemia, and hypocalcemia. The most common serious adverse reactions reported in patients receiving Halaven were neutropenia (4.9%) and pyrexia (4.5%).[2]

Soft tissue sarcoma is a collective term for a diverse group of malignant tumors that occur throughout the soft tissues (fat, muscle, nerves, fibrous tissues and blood vessels) in the body. Approximately 12,000 patients in the United States are diagnosed with soft tissue sarcoma each year, and liposarcoma is one of the most common forms of soft tissue sarcoma. As outcomes are poor for patients with advanced disease, it remains a disease with significant unmet medical need.

Applications seeking approval of Halaven for use in the treatment of soft tissue sarcoma have been submitted in Europe and Japan. Meanwhile, the agent 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.[2] In addition, recent non-clinical studies showed that Halaven is associated with increased vascular perfusion and permeability in tumor cores.[3] Halaven promotes the epithelial state and decreases the capacity of breast cancer cells to migrate.[4] It was first approved in the United States in November 2010 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 including Japan and countries in Europe, the Americas and Asia.

Through this additional approval, Eisai remains committed to providing further clinical evidence for Halaven aimed at maximizing value of the drug as it seeks to contribute further to 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. About Halaven (eribulin mesylate)

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.[3] Halaven promotes the epithelial state and decreases the capacity of breast cancer cells to migrate.[4]

Halaven was first approved as a treatment in the United States in November 2010 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 has been approved in the United States for the treatment of patients with unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen, and applications seeking approval for this potential indication have been submitted in Japan and Europe. Meanwhile, Halaven has been designated as an orphan drug for soft-tissue sarcoma in the United States and Japan.

2. About Soft Tissue Sarcoma

Soft tissue sarcoma is a collective term for a diverse group of malignant tumors that occur throughout the soft tissue (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.

3. About Study 309

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 versus dacarbazine in 452 patients (aged 18 or over) with locally advanced or recurrent and 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 Halaven (1.4 mg/m^2 administered intravenously on Day 1 and Day 8) or dacarbazine (850–1200 mg/m^2 administered intravenously on Day 1) every 21 days until disease progression.

From the results for the study, Halaven demonstrated a statistically significant extension in the study's primary endpoint of overall survival (OS) over the comparator treatment dacarbazine (Halaven median OS: 13.5 months vs dacarbazine median OS: 11.5 months; Hazard Ratio (HR) 0.768 [95% CI=0.618-0.954], p=0.017).[1] Furthermore, in the study's secondary endpoints, there was no statistically significant difference found between Halaven and dacarbazine in either progression-free survival (PFS) (median PFS: 2.6 months in both arms) or progression-free rate at 12 weeks ($PFR12_{wks}$) (Halaven $PFR12_{wks}$: 33% vs dacarbazine $PFR12_{wks}$: 29%).[1]

For patients with liposarcoma, Halaven demonstrated a statistically significant improvement in OS over dacarbazine (Halaven, n=71, median OS: 15.6 months vs dacarbazine, n=72, median OS: 8.4 months; HR 0.51 [95% CI=0.35-0.75]).[2] Additionally, patients treated with Halaven experienced an improvement in PFS over dacarbazine (Halaven median PFS: 2.9 months vs dacarbazine median PFS: 1.7 months; HR 0.52 [95% CI=0.35-0.78]).[2]

The most common adverse reactions (incidence greater than or equal to 25%) in study patients with liposarcoma and leiomyosarcoma treated with Halaven were fatigue (62%), nausea (41%), alopecia (35%), constipation (32%), peripheral neuropathy (29%), abdominal pain (29%) and pyrexia (28%), which was consistent with the known side-effect profile of Halaven.[2] The most common (incidence greater than or equal to 5%) Grade 3-4 laboratory abnormalities reported in patients receiving Halaven were neutropenia (32% vs. 8.9% in the dacarbazine arm), hypokalemia (5.4% vs. 2.8%) and hypocalcemia (5.0% vs. 1.4%). The most common serious adverse reactions reported in patients receiving Halaven were neutropenia (4.9%) and pyrexia (4.5%).[2] The most common adverse reactions resulting in discontinuation of Halaven were fatigue and thrombocytopenia (0.9% each).

For further information on Halaven in the United States, including Important Safety Information (ISI), please visit the Halaven product website (http://www.halaven.com).

[1] Schöffski P et al. Randomized, open-label, multicenter, phase 3 study of eribulin versus dacarbazine in patients (pts) with leiomyosarcoma (LMS) and adipocytic sarcoma (ADI). *American Society of Clinical Oncology annual meeting* 2015; Abstract #LBA10502

[2] Halaven [package insert]. Woodcliff Lake, NJ: Eisai Inc.; 2016.

[3] 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

[4] 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