



Product Fact Sheet

ABOUT HALAVEN® (eribulin mesylate) INJECTION

HALAVEN was approved by the FDA in November 2010 for the treatment of patients with metastatic breast cancer who have previously 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.¹

- Metastatic breast cancer is an advanced stage of the disease that occurs when cancer spreads beyond the breast to other parts of the body. It is estimated approximately 5 percent of women with breast cancer will have metastatic disease at the time of diagnosis and approximately 30 percent of all breast cancer cases will become metastatic.^{2,3} An estimated one in four women with metastatic breast cancer is expected to survive five years.²

HALAVEN was approved in January 2016 following a Priority Review for the treatment of patients with unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen.¹

- HALAVEN received Orphan Drug Designation for advanced soft tissue sarcoma in May 2012. The annual incidence of soft tissue sarcoma, a family of cancers that develop in cells in the soft, supporting tissues of the body, is approximately 30 cases per million of the population – equivalent to less than 1% of all malignant tumors.^{4,5} Liposarcomas, malignancies that arise from fat cells, make up approximately 17% of all cases of soft tissue sarcoma, or about 2,000 new cases each year in the U.S.^{4,6} Soft tissue sarcomas are mostly diagnosed in early-stage or localized disease, and many patients are amenable to complete surgical removal, yet relapse rates can be as high as 50% and outcomes for patients with advanced disease are poor, with median survival around 1 year or less.^{4,7,8}

MECHANISM OF ACTION

Discovered and developed by Eisai, HALAVEN is a synthetic analog of halichondrin B, a natural product that was isolated from the marine sponge *Halichondria okadai*.

First in the halichondrin class, HALAVEN is a microtubule dynamics inhibitor with a distinct binding profile.¹ Based on in vitro studies, HALAVEN exerts its effect via a tubulin-based antimitotic mechanism ultimately leading to apoptotic cell death after prolonged and irreversible mitotic blockage.^{1,9}

In addition, treatment with HALAVEN caused changes in cell structure and gene expression, and decreased migration and invasiveness of human breast cancer cells in vitro.¹ In preclinical models of human breast cancer, HALAVEN treatment was associated with increased vascular perfusion and permeability in the tumor cores, resulting in reduced tumor hypoxia, and changes in the expression of genes in tumor specimens associated with a change in phenotype.¹



IMPORTANT SAFETY INFORMATION¹

Warnings and Precautions

Neutropenia: Severe neutropenia (ANC <500/mm³) lasting > 1 week occurred in 12% of patients with MBC and 12% of patients with liposarcoma or leiomyosarcoma. Febrile neutropenia occurred in 5% of patients with MBC and two patients (0.4%) died from complications. Febrile neutropenia occurred in 0.9% of patients with liposarcoma or leiomyosarcoma and fatal neutropenic sepsis occurred in 0.9% of patients. In patients with MBC with elevated liver enzymes >3 × ULN and bilirubin >1.5 × ULN experienced a higher incidence of Grade 4 neutropenia and febrile neutropenia than patients with normal levels. Monitor complete blood cell counts prior to each dose, and increase the frequency of monitoring in patients who develop Grade 3 or 4 cytopenias. Delay administration and reduce subsequent doses in patients who experience febrile neutropenia or Grade 4 neutropenia lasting > 7 days.

Peripheral Neuropathy: Grade 3 peripheral neuropathy occurred in 8% of patients with MBC (Grade 4 = 0.4%) and 22% developed a new or worsening neuropathy that had not recovered within a median follow-up duration of 269 days (range 25-662 days). Neuropathy lasting > 1 year occurred in 5% of patients with mBC. Grade 3 peripheral neuropathy occurred in 3.1% of patients with liposarcoma and leiomyosarcoma receiving HALAVEN and neuropathy lasting more than 60 days occurred in 58% (38/65) of patients who had neuropathy at the last treatment visit. Patients should be monitored for signs of peripheral motor and sensory neuropathy. Withhold HALAVEN in patients who experience Grade 3 or 4 peripheral neuropathy, until resolution to Grade 2 or less.

See additional Important Safety Information on following pages. For additional information, click [here](#) for the Full Prescribing Information.

EFFICACY AND SAFETY

The FDA approval of HALAVEN® (eribulin mesylate) (1 mg/2 mL) in **third-line metastatic breast cancer** is based on results from the pivotal Phase 3 clinical study, EMBRACE (Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus Eribulin), which showed that patients with metastatic breast cancer treated with Halaven (n=508) experienced a statistically significant improvement in overall survival compared to patients who received a single-agent therapy chosen by their physician (Treatment of Physician's Choice [TPC]: vinorelbine, gemcitabine, capecitabine, taxane, anthracycline, other chemotherapy and hormone therapy) (n=254).¹ Patients in the EMBRACE trial had received at least two chemotherapeutic regimens for the treatment of metastatic disease, and showed signs of progression within 6 months of their latest chemotherapeutic regimen.¹ Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting.¹

The FDA approval of HALAVEN in **advanced liposarcoma** is based on results from the pivotal Phase 3 trial, Study 309, which demonstrated advanced liposarcoma patients treated with Halaven (n=71) experienced a statistically significant and clinically meaningful overall survival benefit and a significant improvement in progression-free survival compared to those treated with dacarbazine (n=72).¹ Patients in Study 309 had documented evidence of unresectable, locally advanced or metastatic liposarcoma (including dedifferentiated, myxoid, round cell and pleomorphic subtypes) or leiomyosarcoma, at least two prior systemic chemotherapies (one of which must have included an anthracycline), and disease progression within 6 months of their most recent chemotherapy regimen.¹

HALAVEN IS THE FIRST AND ONLY SINGLE AGENT TO DEMONSTRATE AN OVERALL SURVIVAL BENEFIT IN EACH OF THESE PRE-TREATED, DIFFICULT-TO-TREAT CANCERS (Third-Line Metastatic Breast Cancer and Advanced Liposarcoma)

Twice-proven OS Benefit¹

- In the EMBRACE trial, patients with metastatic breast cancer, regardless of receptor status, who received Halaven survived a median of 13.1 months compared to 10.6 months for patients who received TPC (HR 0.81; 95% CI 0.66-0.99; p=0.041). An updated OS analysis conducted when 77% of events had occurred was consistent with the primary analysis (13.2 months vs. 10.6 months).
- In Study 309, liposarcoma patients who received Halaven experienced a median overall survival of 15.6 months compared to 8.4 months for those treated with dacarbazine (HR 0.51; 95% CI 0.35-0.75).

Longer PFS in Advanced Liposarcoma

- Patients with liposarcoma who received Halaven in Study 309 also experienced a longer median progression-free survival (PFS), a secondary endpoint, compared to those who received dacarbazine (median 2.9 months vs. 1.7 months; HR 0.52; 95% CI: 0.35-0.78).¹

More About Study 309¹

In Study 309, Halaven demonstrated a statistically significant improvement in overall survival (OS) compared to dacarbazine. Median OS in all treated patients was 13.5 months with Halaven vs. 11.3 months with dacarbazine (HR 0.75; 95% CI: 0.61-0.94; p=0.011), and PFS was 2.6 months with Halaven vs. 2.6 months with dacarbazine (HR 0.86; 95% CI: 0.69-1.06). The treatment effects of Halaven were limited to patients with liposarcoma, based on pre-planned, exploratory subgroup analyses of OS and PFS. There was no evidence of efficacy of Halaven in patients with advanced or metastatic leiomyosarcoma.

IMPORTANT SAFETY INFORMATION (CONTINUED)¹

Embryo-Fetal Toxicity: HALAVEN can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with HALAVEN and for at least 2 weeks following the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with HALAVEN and for 3.5 months following the final dose.

QT Prolongation: Monitor for prolonged QT intervals in patients with congestive heart failure, bradyarrhythmias, drugs known to prolong the QT interval, and electrolyte abnormalities. Correct hypokalemia or hypomagnesemia prior to initiating HALAVEN and monitor these electrolytes periodically during therapy. Avoid in patients with congenital long QT syndrome.

Adverse Reactions: In patients with liposarcoma and leiomyosarcoma receiving HALAVEN the most common adverse reactions ($\geq 25\%$) reported in patients receiving HALAVEN were fatigue (62%), nausea (41%), alopecia (35%), constipation (32%), peripheral neuropathy (29%), abdominal pain (29%), and pyrexia (28%). The most common ($\geq 5\%$) Grade 3-4 laboratory abnormalities reported in patients receiving HALAVEN were neutropenia (32%), hypokalemia (5.4%), and hypocalcemia (5%). Neutropenia (4.9%) and pyrexia (4.5%) were the most common serious adverse reactions. The most common adverse reactions resulting in discontinuation were fatigue and thrombocytopenia (0.9% each).

See additional Important Safety Information on following pages. For additional information, click [here](#) for the Full Prescribing Information.

DOSING AND ADMINISTRATION¹

HALAVEN® (eribulin mesylate) is administered 1.4mg/m² intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle. It is available in vials containing 1 mg of eribulin mesylate as a 0.5mg/mL solution in ethanol:water (5:95).

ACCESS AND AFFORDABILITY

Eisai strongly believes it is important that patients have access to medicines from which they may benefit and, as such, we are committed to working with payers to ensure our products are available to those who need them.

To assist eligible patients with access to their medication, Eisai offers patients a HALAVEN Savings Program and Patient Assistance Program.* Patients can visit www.HalavenReimbursement.com/savings to learn more and download an enrollment form now.

*Restrictions apply. Not available to patients enrolled in federal or state healthcare programs, including Medicare, Medicaid, Medigap, VA, DoD or TRICARE. Please refer to complete [Eligibility Criteria](#).

MANUFACTURING AND U.S. MARKETING

HALAVEN, currently approved in approximately 60 countries for various indications, was discovered and developed by Eisai. HALAVEN is manufactured and marketed in the U.S. by Eisai Inc.

FOR MORE INFORMATION ABOUT HALAVEN® (eribulin mesylate) INJECTION

For additional product information, please call Eisai Medical Information at 1-888-274-2378 or visit www.Halaven.com.

IMPORTANT SAFETY INFORMATION (CONTINUED)¹

Adverse Reactions: In patients with MBC receiving HALAVEN the most common adverse reactions ($\geq 25\%$) were neutropenia (82%), anemia (58%), asthenia/fatigue (54%), alopecia (45%), peripheral neuropathy (35%), nausea (35%), and constipation (25%). Febrile neutropenia (4%) and neutropenia (2%) were the most common serious adverse reactions. The most common adverse reaction resulting in discontinuation was peripheral neuropathy (5%).

Use in Specific Populations:

Lactation: Because of the potential for serious adverse reactions in breastfed infants from eribulin mesylate, advise women not to breastfeed during treatment with HALAVEN and for 2 weeks after the final dose.

Hepatic and Renal Impairment: A reduction in starting dose is recommended for patients with mild or moderate hepatic impairment and/or moderate or severe renal impairment.

For more information about HALAVEN® (eribulin mesylate), click [here](#) for the full Prescribing Information.

¹ Halaven® [package insert]. Woodcliff Lake, NJ: Eisai Inc.; 2016.

² SEER Cancer Statistics Factsheets: Breast Cancer. National Cancer Institute. Bethesda, MD. <http://seer.cancer.gov/statfacts/html/breast.html>

³ O'Shaughnessy J. Extending Survival with Chemotherapy in Metastatic Breast Cancer. *The Oncologist*. 2005;10(3):20-29.

http://theoncologist.alphamedpress.org/content/10/suppl_3/20

⁴ American Cancer Society. What is a soft tissue sarcoma? March 2015. <http://www.cancer.org/cancer/sarcoma-adultsofttissuecancer/detailedguide/sarcoma-adult-soft-tissue-cancer-soft-tissue-sarcoma>

⁵ Fletcher et al. World Health Organization Classification of Tumours of Soft Tissue and Bone (4th Edition). Lyon: IARC Press, 2013

⁶ SEER Cancer Statistics Review 1975-2012: Soft tissue sarcoma. National Cancer Institute. Bethesda, MD: http://seer.cancer.gov/csr/1975_2012/results_merged/sect_34_soft_tissue_sarcomas.pdf. Accessed: December 2015.

⁷ Pollock R. Soft tissue sarcomas: A volume in the American Cancer Society atlas of clinical oncology. 2002.

⁸ Storm HH et al. Survival of adult patients with cancer of soft tissues or bone in Europe. *Eur J Cancer*. 1998;34(14):2212-2217.

⁹ Towle MJ, Salvator KA, Wels BF, et al. Eribulin induces irreversible mitotic blockage: Implications of cell-based pharmacodynamics for in vivo efficacy under intermittent dosing conditions. *Cancer Res*. 2011;71(12):496-505.