COMMUNITY GROUPS

For patients

➤ Breastcancer.org  www.breastcancer.org
  Discussion Board:  http://community.breastcancer.org
  An oncologist specializing in breast cancer founded Breastcancer.org to help women and their
  loved ones make sense of the complex medical and personal information surrounding the disease,
  enabling them to make the best decisions for their lives.

➤ Breast Friends, Inc  www.breastfriends.org
  Phone: 888-386-8048  |  E-mail:  See Web site
  Breast Friends provides one-on-one and family emotional support for patients living with
  breast cancer.

➤ CancerCare  www.cancercare.org
  Phone: 800-813-4673  |  E-mail:  info@cancercare.org
  CancerCare provides free professional support services to anyone affected by cancer, including
  patients, caregivers, children, loved ones, and the bereaved.

➤ Cancer Support Community  www.cancersupportcommunity.org
  Phone: 888-793-9355  |  E-mail:  help@cancersupportcommunity.org
  Cancer Support Community strives to answer the social and emotional needs of those affected
  by cancer and ensures that all affected by advanced breast cancer are empowered by knowledge,
  strengthened by action, and sustained by their community.

➤ Living Beyond Breast Cancer  www.lbbc.org
  Phone: 610-645-4567  |  E-mail:  mail@lbbc.org
  Living Beyond Breast Cancer (LBBC) provides services designed to help improve quality of life for
  women who are newly diagnosed, in treatment, in recovery, years beyond their diagnosis, or living
  with metastatic breast cancer (MBC), as well as resources for family, friends, and caregivers.

➤ The Metastatic Breast Cancer Alliance  www.MBCAlliance.org
  E-mail:  mbcalliancesocial@gmail.com
  The Metastatic Breast Cancer Alliance is dedicated to improving the lives of and outcomes for
  those living with MBC and their families through increasing awareness and education about the
  disease and advancing policy and strategic coordination of research funding specifically focused
  on metastasis that has the potential to extend life, enhance quality of life and ultimately to cure.

Please see list of additional community groups on next page.

Please see Safety Information and HALAVEN full Prescribing Information on the following pages.
Metastatic Breast Cancer Network  www.mbcn.org
Phone: 888-500-0370 | E-mail: mbcn@mbcn.org
The Metastatic Breast Cancer Network (MBCN) is a national, patient-led organization that provides support, education, and information to women and men living with the disease. MBCN encourages patients and caregivers to raise their voices to raise awareness and demand focused research to extend lives.

METAvisor Research and Support  www.metavivor.org
Phone: 410-491-5760 | E-mail: info@metavivor.org
METAvisor is a nonprofit organization run entirely by volunteers, most of whom have MBC. Since 2009, METAvisor’s mission has been to provide support and fund research to end death caused by MBC.

National Coalition for Cancer Survivorship  www.canceradvocacy.org
Phone: 301-650-9127 | E-mail: info@canceradvocacy.org
Founded by and for cancer survivors, the National Coalition for Cancer Survivorship (NCCS) advocates for quality cancer care for all people touched by cancer and provides tools that empower people to advocate for themselves.

Young Survival Coalition  www.youngsurvival.org
Phone: 877-972-1011 | E-mail: info@youngsurvival.org
Founded by young survivors, Young Survival Coalition (YSC) advocates for and supports young women with breast cancer. MBC programs include monthly networking calls, a metastatic treatment navigator, online community board forums, resources, and SurvivorLink one-on-one support.

For family and friends

American Cancer Society  www.cancer.org/treatment/caregivers/index
Phone: 800-227-2345
The American Cancer Society (ACS) is a nationwide health organization with more than a century of history in supporting those with cancer. The ACS also provides numerous tools and resources to help family and friends who may be acting as caregivers.

Caregiver Action Network  www.caregiveraction.org
Phone: 202-454-3970 | E-mail: info@caregiveraction.org
The Caregiver Action Network serves a broad spectrum of family caregivers ranging from the parents of children with special needs, to the families and friends of wounded soldiers; from a young couple dealing with a diagnosis of MS, to adult children caring for parents with Alzheimer’s disease.

MyLifeLine.org Cancer Foundation  www.mylifeline.org
Phone: 720-883-8715 | E-mail: support@mylifeline.org
MyLifeLine.org encourages cancer patients and caregivers to create free, customized Web sites. Each personalized page helps build an online support community of family and friends to foster connection, inspiration, and healing.

Please see Safety Information and HALAVEN full Prescribing Information on the following pages.
Who is HALAVEN® for?
HALAVEN is a prescription medicine used to treat patients with metastatic breast cancer. HALAVEN is for patients who have already received at least 2 other types of anticancer medicines for their breast cancer once it has spread to other parts of the body. Previous therapy should have included an anthracycline and a taxane for either early or advanced breast cancer.

What safety information do I need to know about HALAVEN?

Neutropenia (Decreased White Blood Cells)
- Your health care provider should do a blood test to monitor your blood cells before you receive each dose of HALAVEN, and should monitor you more often if you develop lower white blood cells.
- If you develop severe neutropenia lasting longer than 7 days or neutropenia with a fever, your next dose of HALAVEN should be delayed and reduced. In a clinical trial, severe neutropenia occurred in 57% of patients who received HALAVEN and lasted more than 1 week in 12% of patients.
- Neutropenia with a fever occurred in 5% of patients; 2 patients died from complications of neutropenia with a fever.
- Neutropenia with a fever can result in serious infections that could lead to hospitalization or death. Call your health care provider immediately if you have any of the following symptoms: fever (temperature above 100.5°F), chills, coughing, and burning or pain when you urinate.

Peripheral Neuropathy (Nerve Problems)
- HALAVEN can cause numbness, tingling, or burning in your hands and feet (peripheral neuropathy). You should be monitored closely for signs of neuropathy. If you develop severe neuropathy, treatment with HALAVEN should be delayed until the neuropathy improves and the next dose of HALAVEN should be reduced.
- Severe peripheral neuropathy occurred in 8% of patients who received HALAVEN. Neuropathy lasting more than 1 year occurred in 5% of patients. Twenty-two percent of patients developed a new or worsening neuropathy that had not recovered after an average of 269 days.
- Peripheral neuropathy was the most common side effect that caused patients to stop taking HALAVEN.

Pregnancy and Nursing
- HALAVEN may harm your unborn baby. Avoid becoming pregnant while you are receiving HALAVEN. Tell your health care provider right away if you become pregnant or think you are pregnant while you are receiving HALAVEN.
- It is not known if HALAVEN passes into your breast milk. You and your health care provider should decide if you will take HALAVEN or breast-feed. You should not do both.

Please see additional Safety Information and HALAVEN full Prescribing Information on the following pages.
Safety Information (cont’d)

QT Prolongation (Heartbeat Changes)

➤ HALAVEN can cause changes in your heartbeat. This can cause irregular heartbeats that may lead to death.

➤ Before you receive HALAVEN, tell your health care provider if you have heart problems, including a problem called “congenital long QT syndrome”.

➤ Your health care provider will decide if you need heart monitoring (electrocardiogram or ECG) or blood tests during your treatment with HALAVEN to watch for this problem.

Pre-existing Liver and/or Kidney Problems

➤ Before you receive HALAVEN, tell your health care provider if you have liver or kidney problems. A lower starting dose of HALAVEN is recommended in patients with mild or moderate liver problems, and/or moderate or severe kidney problems.

Most Common Side Effects

➤ The most common side effects reported in ≥25% of patients receiving HALAVEN were low white blood cells; low red blood cells; weakness/tiredness; hair loss; numbness, tingling, or burning in the hands and feet; nausea; and constipation.

➤ The most common serious side effects reported in patients receiving HALAVEN were neutropenia with or without a fever.

Please see additional Safety Information on the previous page and HALAVEN full Prescribing Information on the following pages.
HALAVEN® (eribulin mesylate) Injection

**For intravenous administration**

**Initial US Approval: 2010**

**INDICATIONS AND USAGE**

HALAVEN is a microtubule inhibitor indicated 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).

**Dosage and Administration**

- **Recommended Dose:** 1.4 mg/m² intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle (2.1).

**Dose Modification**

- **Recommended dose delays**:
  - ANC < 1,000/mm³
  - Platelets < 75,000/mm³
  - Grade 3 or 4 non-hematological toxicities.
  - The Day 8 dose may be delayed for a maximum of 1 week.
  - The Day 8 dose may be delayed for a maximum of 2 weeks later.

**Dose adjustment**:

- If toxicities do not resolve or improve to ≤ Grade 2 severity by Day 15, omit the dose.
- If toxicities resolve or improve to ≤ Grade 2 severity by Day 15, administer HALAVEN at a reduced dose and initiate the next cycle no sooner than 2 weeks later.

**Contraindications**

- **None.**

**Warnings and Precautions**

- **Neutropenia:** Monitor peripheral blood cell counts and adjust dose as appropriate (2.2, 5.1, 6).
- **Peripheral Neuropathy:** Monitor for signs of neuropathy. Manage with dose delay and adjustment (2.2, 5.2, 6).
- **Embryo-Fetal Toxicity:** Fetal harm can occur when administered to a pregnant woman (5.3) (6.1).
- **QT Prolongation:** Monitor for prolonged QT intervals in patients with congestive heart failure, bradycardia, or drug-induced QT prolongation (5.4).

**Adverse Reactions**

- The most common adverse reactions (incidence ≥25%) were neutropenia, anemia, asthenia/fatigue, alopecia, peripheral neuropathy, nausea, and constipation (6).

**How Supplied/Storage and Handling**

HALAVEN capsules contain eribulin mesylate, lactose monohydrate, microcrystalline cellulose, sodium stearyl fumarate, and magnesium stearate. Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP-controlled room temperature].

**Full Prescribing Information**

- **Sections or subsections omitted from the full prescribing information are not listed.**

**Recent Major Changes**

- **Dose Modification:**
  - Do not administer HALAVEN on Day 1 or Day 8 for any of the following:
    - ANC < 1,000/mm³
    - Platelets < 75,000/mm³
    - Grade 3 or 4 non-hematological toxicities.
  - The Day 8 dose may be delayed for a maximum of 1 week.
  - The Day 8 dose may be delayed for a maximum of 2 weeks later.

- **Recommended dose delays**:
  - ANC < 1,000/mm³
  - Platelets < 75,000/mm³
  - Grade 3 or 4 non-hematological toxicities.
  - The Day 8 dose may be delayed for a maximum of 1 week.
  - The Day 8 dose may be delayed for a maximum of 2 weeks later.
  - If toxicities do not resolve or improve to ≤ Grade 2 severity by Day 15, omit the dose.
  - If toxicities resolve or improve to ≤ Grade 2 severity by Day 15, administer HALAVEN at a reduced dose and initiate the next cycle no sooner than 2 weeks later.

- **Recommended dose reductions**:
  - If a dose has been delayed for toxicity and toxicities have recovered to Grade 2 severity or less, resume HALAVEN at a reduced dose as set out in Table 1.
  - Do not re-escalate HALAVEN dose after it has been reduced.
Table 1 Recommended Dose Reductions

<table>
<thead>
<tr>
<th>Event Description</th>
<th>Recommended HALAVEN Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Permanently reduce the 1.4 mg/m² HALAVEN dose for any of the following:</strong></td>
<td></td>
</tr>
<tr>
<td>ANC &lt;500/mm³ for &gt;7 days</td>
<td></td>
</tr>
<tr>
<td>ANC &lt;1,000/mm³ with fever or infection</td>
<td></td>
</tr>
<tr>
<td>Platelets &lt;25,000/mm³</td>
<td>1.1 mg/m²</td>
</tr>
<tr>
<td>Platelets &lt;50,000/mm³ requiring transfusion</td>
<td></td>
</tr>
<tr>
<td>Non-hematologic Grade 3 or 4 toxicities</td>
<td></td>
</tr>
<tr>
<td>Omission or delay of Day 8 HALAVEN dose in previous cycle for toxicity</td>
<td></td>
</tr>
<tr>
<td>Occurrence of any event requiring permanent dose reduction while receiving 1.1 mg/m²</td>
<td>0.7 mg/m²</td>
</tr>
<tr>
<td>Occurrence of any event requiring permanent dose reduction while receiving 0.7 mg/m²</td>
<td>Discontinue HALAVEN</td>
</tr>
</tbody>
</table>

ANC = absolute neutrophil count.

Toxicities graded in accordance with National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

2.3 Instructions for Preparation and Administration

Aseptically withdraw the required amount of HALAVEN from the single-use vial and administer undiluted or diluted in 100 mL of 0.9% Sodium Chloride Injection, USP.

Do not dilute in or administer through an intravenous line containing solutions with dextrose.

Do not administer in the same intravenous line concurrent with the other medicinal products.

Store undiluted HALAVEN in the syringe for up to 4 hours at room temperature or for up to 24 hours under refrigeration (40°F or 4°C). Store diluted solutions of HALAVEN for up to 4 hours at room temperature or up to 24 hours under refrigeration.

Discard unused portions of the vial.

3 DOSAGE FORMS AND STRENGTHS

HALAVEN (eribulin mesylate) Injection, 1 mg/2 mL (0.5 mg/mL).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Neutropenia

Severe neutropenia (ANC <500/mm³) lasting more than one week occurred in 12% (62/503) of patients in Study 1, leading to discontinuation in <1% of patients (see Adverse Reactions (6)). Patients with alanine aminotransferase or aspartate aminotransferase > 3 × ULN (upper limit of normal) experienced a higher incidence of Grade 4 neutropenia and febrile neutropenia than patients with normal aminotransferase levels. Patients with bilirubin > 1.5 × ULN also had a higher incidence of Grade 4 neutropenia and febrile neutropenia.

Monitor complete blood counts prior to each dose, increase the frequency of monitoring in patients who develop Grade 3 or 4 cytopenias. Delay administration of HALAVEN and reduce subsequent doses in patients who experience febrile neutropenia or Grade 4 neutropenia lasting longer than 7 days (see Dosage and Administration (2.3)). Clinical studies of HALAVEN did not include patients with baseline neutrophil counts below 1,500/mm³.

5.2 Peripheral Neuropathy

Grade 3 peripheral neuropathy occurred in 8% (40/503) of patients, and Grade 4 in 0.4% (2/503) of patients in Study 1. Peripheral neuropathy was the most common serious adverse reaction reported in patients receiving HALAVEN. Grade 3 peripheral neuropathy occurred in 8% (40/503) of patients, and Grade 4 in 0.4% (2/503) of patients in Study 1, and 29% (144/503) of patients experienced Grade 4 neutropenia.

Neuropathy lasting more than one year occurred in 5% (25/503) of patients. Twenty-two percent (109/503) of patients developed a new or worsening neuropathy that had not recovered within a previous cycle for toxicity. Of patients developed a new or worsening neuropathy that had not recovered within a previous cycle for toxicity. Clinical studies of HALAVEN did not include patients with baseline neuropathic symptoms.

5.3 Embryo-Fetal Toxicity

There are no adequate and well-controlled studies of HALAVEN in pregnant women. HALAVEN is a microtubule inhibitor; therefore, it is expected to cause fetal harm when administered to a pregnant woman. Embryo-fetal toxicity and teratogenicity occurred in rats that received eribulin mesylate at approximately half of the recommended human dose based on body surface area. If this drug is used during pregnancy, or if a patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus (see Use in Specific Populations (8.1)).

5.4 QT Prolongation

In an uncontrolled open-label ECG study in 26 patients, QT prolongation was observed on Day 8, independent of eribulin concentration, with no QT prolongation observed on Day 1. ECG monitoring is recommended if therapy is initiated in patients with congestive heart failure, bradyarrhythmias, drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics, and electrolyte abnormalities. Correct hypokalemia or hypomagnesemia prior to initiating HALAVEN and monitor these electrolytes periodically during therapy. Avoid HALAVEN in patients with congenital long QT syndrome.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in clinical practice.

The following adverse reactions are discussed in detail in other sections of the labeling:

- Neutropenia (see Warnings and Precautions (5.1)).
- Peripheral neuropathy (see Warnings and Precautions (5.2)).
- QT interval prolongation (see Warnings and Precautions (5.4)).

In clinical trials, HALAVEN has been administered to 1,222 patients with multiple tumor types, including 240 patients exposed to HALAVEN for 6 months or longer. The majority of the 1,222 patients were women (82%) with a median age of 58 years (range: 26 to 91 years). The racial and ethnic distribution was Caucasian (83%), Black (5%), Asian (2%), and other (5%).

The adverse reactions described in Table 2 were identified in 750 patients treated in Study 1 (see Clinical Studies (14)). In Study 1, patients were randomized (2:1) to receive either HALAVEN (1.4 mg/m² on Days 1 and 8 of a 21-day cycle) or single agent treatment chosen by their physician (control group). A total of 503 patients received HALAVEN, and 247 patients in the control group received therapy consisting of chemotherapy [total 97% (anthracyclines 10%, capecitabine 18%, gemcitabine 19%, taxanes 15%, vinorelbine 25%, other chemotherapies 10%)] or hormonal therapy (3%). The median duration of exposure was 118 days for patients receiving HALAVEN and 63 days for patients receiving control therapy. Table 2 reports the most common adverse reactions occurring in at least 10% of patients in either group.

Table 2 Adverse Reactions with a Per-Patient Incidence of at Least 10% in Study 1

<table>
<thead>
<tr>
<th>MedDRA ver 10.0</th>
<th>HALAVEN n=503</th>
<th>Control Group n=247</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>≥ Grade 3</td>
<td>All Grades</td>
</tr>
<tr>
<td><strong>Blood and Lymphatic System Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>82%</td>
<td>57%</td>
</tr>
<tr>
<td>Anemia</td>
<td>58%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>35%</td>
<td>8%</td>
</tr>
<tr>
<td>Headache</td>
<td>13%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>25%</td>
<td>1%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18%</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>35%</td>
<td>1%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia/Myalgia</td>
<td>22%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Back pain</td>
<td>16%</td>
<td>1%</td>
</tr>
<tr>
<td>Bone pain</td>
<td>12%</td>
<td>2%</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>11%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight decreased</td>
<td>21%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>20%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic, and mediastinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>14%</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>16%</td>
<td>4%</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>45%</td>
<td>NA*</td>
</tr>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>10%</td>
<td>1%</td>
</tr>
</tbody>
</table>

* based upon laboratory data.

NA* includes neuropathy peripheral, neuropathy, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, and paraesthesia.

Not applicable. (Grading system does not specify > Grade 2 for alopecia.

Cytophenias: Grade 3 neutropenia occurred in 28% (143/503) of patients who received HALAVEN in Study 1, and 29% (144/503) of patients experienced Grade 4 neutropenia. Febrile neutropenia occurred in 5% (23/503) of patients; two patients (0.4%) died from complications of febrile neutropenia. Dose reduction due to neutropenia was required in 12% (62/503) of patients and discontinuation was required in <1% of patients. The mean
time to nadir was 13 days and the mean time to recovery from severe neutropenia (<500/mm³) was 8 days. Grade 3 or greater thrombocytopenia occurred in 1% (7/753) of patients. G-CSF (granulocyte colony-stimulating factor) or GM-CSF (granulocyte–macrophage colony-stimulating factor) was used in 19% of patients who received HALAVEN.

### 8.6 Hepatic Impairment
Administration of HALAVEN at a dose of 1.1 mg/m² to patients with mild hepatic impairment and 0.7 mg/m² to patients with moderate hepatic impairment resulted in similar exposure to eribulin as a dose of 1.4 mg/m² to patients with normal hepatic function. Therefore, a lower starting dose of 1.1 mg/m² is recommended for patients with mild hepatic impairment (Child-Pugh A) and 0.7 mg/m² is recommended for patients with moderate hepatic impairment (Child-Pugh B). HALAVEN was not studied in patients with severe hepatic impairment (Child-Pugh C) [see Dosage and Administration (2.1), Clinical Pharmacology (12.3)].

### 8.7 Renal Impairment
For patients with moderate or severe renal impairment (CrCl 15-49 mL/min), reduce the starting dose to 1.1 mg/m² [see Dosage and Administration (2.1), Clinical Pharmacology (12.3)].

### 10 OVERDOSAGE
Overdosage of HALAVEN has been reported at approximately 4 times the recommended dose, which resulted in Grade 3 neutropenia lasting seven days and a Grade 3 hypersensitivity reaction lasting one day. There is no known antidote for HALAVEN overdose.

### 11 DESCRIPTION
HALAVEN (eribulin mesylate) injection is a non-taxane microtubule dynamics inhibitor. Eribulin mesylate is a synthetic analogue of halichondrin B, a product isolated from the marine sponge Halichondria okadaei. The chemical name for eribulin mesylate is 11,15,18,21,24,26-Tripyrano[4,3-i][H]furo[2',3':5,6]hexacosahydro-3-methoxy-26-methyl-20,27-bis(methylene)-pyranoyl-4,3-b-dl[dioxycyclopropacin-5(H)-one, 2-[2(S)-3-amino-2-hydroxypropyl]-hexacosahydro-3-methoxy-26-methyl-20,27-bis(methylene)-, (2R,3R,3a,7a,8a,9,10a,11S,12R,13aR,13bS,15S,1S,18S,21S,24S,26R,28R,29aS)-methanesulfonate (salt). It has a molecular weight of 828.0 (729.9 for free base). The empirical formula is C_{40}H_{59}NO_{11}•CH_{4}O_{3}S. Eribulin mesylate has the following structural formula:

![Eribulin mesylate structural formula]

HALAVEN is a clear, colorless, sterile solution for intravenous administration. Each vial contains 1 mg of eribulin mesylate as a 0.5 mg/mL solution in ethanol: water (5:95).

### 12 CLINICAL PHARMACOLOGY

#### 12.1 Mechanism of Action
Eribulin inhibits the growth phase of microtubules without affecting the shortening phase and sequesters tubulin into nonproductive aggregates. Eribulin exerts its effects via a tubulin-based antimotic mechanism leading to G/M cell-cycle block, disruption of mitotic spindles, and, ultimately, apoptotic cell death after prolonged mitotic blockage.

#### 12.3 Pharmacokinetics
The pharmacokinetics (PK) of eribulin is linear with a mean elimination half-life of approximately 40 hours, a mean volume of distribution of 43 L/m² to 114 L/m² and mean clearance of 1.18 L/hr/m² to 2.42 L/hr/m² over the dose range of 0.25 mg/m² to 4.0 mg/m². The human plasma protein binding of eribulin at concentrations of 100 ng/mL to 1.000 ng/mL ranges from 49% to 65%. Eribulin exposure after multiple dosing is comparable to that following a single dose. No accumulation of eribulin is observed with weekly administration.

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**Eribulin is not expected to alter the plasma concentrations of drugs that are substrates of these enzymes** [see Clinical Pharmacology (12.3)].
**14 CLINICAL STUDIES**

Study 1 was an open-label, randomized, multicenter trial of 762 patients with metastatic breast cancer who received at least two chemotherapy regimens for the treatment of metastatic disease and experienced disease progression within 6 months of their last chemotherapy regimen. Patients were required to receive prior anthracycline- and taxane-based chemotherapy for adjuvant or metastatic disease. Patients were randomized (2:1) to receive HALAVEN (n=508) or a single agent therapy selected prior to randomization (control arm, n=254). Randomization was stratified by geographic region, HER2/neu status, and prior capecitabine exposure. HALAVEN was administered at a dose of 1.4 mg/m² on Days 1 and 8 of a 21-day cycle. HALAVEN-treated patients received a median of 5 cycles (range: 1 to 23 cycles) of therapy. Control arm therapy consisted of 97% chemotherapy (26% vinorelbine, 18% gemcitabine, 18% capecitabine, 16% taxane, 9% anthracycline, 10% other chemotherapy), and 3% hormonal therapy. The main efficacy outcome was overall survival.

Patient demographic and baseline characteristics were comparable between the treatment arms. The median age was 55 (range: 27 to 85 years) and 92% were White. Sixty-four percent of patients were enrolled in North America/Western Europe/Australia, 25% in Eastern Europe/Russia, and 11% in Latin America/South Africa. Ninety-one percent of patients had a baseline ECOG performance status of 0 or 1. Tumor prognostic characteristics, including estrogen receptor status (positive: 67%, negative: 28%), progesterone receptor status (positive: 49%, negative: 39%), HER2/neu receptor status (positive: 16%, negative: 74%), triple negative status (ER-, PR-, HER2/neu-: 19%), presence of visceral disease (82%, including 60% liver and 38% lung) and bone disease (61%), and number of sites of metastases (greater than two: 50%), were also similar in the HALAVEN and control arms. Patients received a median of four prior chemotherapy regimens in both arms.

In Study 1, a statistically significant improvement in overall survival was observed in patients randomized to the HALAVEN arm compared to the control arm (see Table 3). An updated, unplanned survival analysis, conducted when 77% of events had been observed (see Figure 1), was consistent with the primary analysis. In patients randomized to HALAVEN, the objective response rate by the RECIST criteria was 11% (95% CI: 8.6%, 14.3%) and the median response duration was 4.2 months (95% CI: 3.8, 5.0 months).

<table>
<thead>
<tr>
<th>Overall Survival</th>
<th>HALAVEN (n=508)</th>
<th>Control Arm (n=254)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of deaths</td>
<td>274</td>
<td>148</td>
</tr>
<tr>
<td>Median, months (95% CI)</td>
<td>13.1 (11.8, 14.3)</td>
<td>10.6 (9.3, 12.5)</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>0.81 (0.66, 0.99)</td>
<td>P-value* 0.041</td>
</tr>
<tr>
<td>Updated survival analysis</td>
<td>Number of deaths 386</td>
<td>203</td>
</tr>
<tr>
<td>Median, months (95% CI)</td>
<td>13.2 (12.1, 14.4)</td>
<td>10.6 (9.2, 12.0)</td>
</tr>
</tbody>
</table>

CI = confidence interval
* Based on Cox proportional hazards model stratified by geographic region, HER2 status, and prior capecitabine therapy.

**Figure 1 Updated Overall Survival Analysis for Study 1**

**13 NONCLINICAL TOXICOLOGY**

**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Carcinogenicity studies have not been conducted with eribulin mesylate. Eribulin mesylate was not mutagenic in in vitro bacterial reverse mutation assays (Ames test). Eribulin mesylate was positive in mouse lymphoma mutagenesis assays, and was clastogenic in an in vivo rat bone marrow micronucleus assay.

The effects of HALAVEN on human fertility are unknown. Fertility studies have not been conducted with eribulin mesylate in humans or animals. However, nonclinical findings in repeated-dose dog and rat toxicology studies suggest that male fertility may be compromised by treatment with eribulin mesylate. Rats exhibited testicular toxicity (hypocellularity of seminiferous epithelium with hypospermatia/aspermia) following dosing with eribulin mesylate at or above 0.43 times the recommended human dose (mg/m²) given once weekly for 3 weeks, or at or above 0.21 times the recommended human dose (mg/m²) given once weekly for 3 out of 5 weeks, repeated for 6 cycles. Testicular toxicity was also observed in dogs given 0.84 times the recommended human dose (mg/m²) weekly for 5 out of 5 cycles, repeated for 6 cycles.

**10 CLINICAL TOXICOLOGY**

Unchanged eribulin was the major circulating species in plasma following administration of 14C-eribulin to patients. Metabolite concentrations represented <0.1% of parent compound, confirming that there are no major human metabolites of eribulin. Cytochrome P450 3A4 (CYP3A4) negligibly metabolizes eribulin in vitro.

**14 Elimination**

Eribulin is eliminated primarily in feces unchanged. After administration of 14C-eribulin to patients, approximately 82% of the dose was eliminated in feces and 9% in urine. Unchanged eribulin accounted for approximately 88% and 91% of the dose in feces and urine, respectively.

**Effects of Age, Gender, and Race**

Based on a population pharmacokinetic analysis with data collected from 340 patients, gender, race, and age do not have a clinically meaningful effect on the PK of eribulin.

**Drug Interactions**

**Effect of Other Drugs on HALAVEN**

The effect of a strong CYP3A4 inhibitor and a P-gp inhibitor, ketoconazole, on the PK of eribulin was studied in a crossover trial of 12 patients with advanced solid tumors. No clinically relevant PK interaction was observed when HALAVEN was administered with or without ketoconazole (the geometric mean ratio of the AUC: 1.10, 90% CI: 0.91, 1.34).

**Effect of HALAVEN on Other Drugs**

Eribulin shows no induction potential for CYP1A2, CYP2C8, CYP2C19, and CYP3A, and no clastogenic in an in vivo rat bone marrow micronucleus assay. Eribulin mesylate was not mutagenic in bacterial reverse mutation assays (Ames test). No significant inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP2E1 was detected in human hepatocytes. Eribulin inhibits CYP3A4 activity in human liver microsomes, but it is unlikely that eribulin will substantially increase the plasma levels of CYP3A4 substrates. No significant inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP2E1 was detected in primary human hepatocytes, and it is unlikely that eribulin will affect plasma levels of drugs that are substrates of CYP enzymes. Eribulin is a substrate and a weak inhibitor of the drug efflux transporter P-gp in vitro.

**Specific Populations**

**Hepatic Impairment**

A study evaluated the PK of eribulin in patients with mild (Child-Pugh A; n=7) and moderate (Child-Pugh B; n=5) hepatic impairment. Compared to patients with normal hepatic function (n=6), eribulin exposures increased 1.8-fold and 2.5-fold in patients with mild and moderate hepatic impairment, respectively. Administration of HALAVEN at a dose of 1.1 mg/m² to patients with mild hepatic impairment and 0.7 mg/m² to patients with moderate hepatic impairment resulted in similar exposure to eribulin as a dose of 1.4 mg/m² to patients with normal hepatic function [see Dosage and Administration (2.1), Use in Specific Populations (8.6)].

**Renal Impairment**

A study evaluated the PK of eribulin in patients with moderate (CrCl: 50-80 mL/min; n=7) and severe (CrCl: <50 mL/min; n=6) renal impairment. Compared to patients with normal renal function (CrCl > 80 mL/min; n=6), patients with moderate and severe renal impairment have 1.5-fold higher eribulin dose-normalized exposures. However for patients with mild renal impairment the data indicate no dose adjustment is necessary [see Dosage and Administration (2.1), Use in Specific Populations (8.7)].

**12.6 Cardiac Electrophysiology**

The effect of HALAVEN on the QTc interval was assessed in an open-label, uncontrolled, multicenter, single-arm dedicated QT trial. A total of 26 patients with solid tumors received 1.4 mg/m² of HALAVEN on Days 1 and 8 of a 21-day cycle. A delayed QTc prolongation was observed on Day 8, with no prolongation observed on Day 1. The maximum mean QTcF change from baseline (95% upper confidence interval) was 11.4 (19.5) ms.

**10 Metabolism**

Eribulin mesylate was not mutagenic in in vitro bacterial reverse mutation assays (Ames test). Eribulin mesylate was positive in mouse lymphoma mutagenesis assays, and was clastogenic in an in vivo rat bone marrow micronucleus assay.

The effects of HALAVEN on human fertility are unknown. Fertility studies have not been conducted with eribulin mesylate in humans or animals. However, nonclinical findings in repeated-dose dog and rat toxicology studies suggest that male fertility may be compromised by treatment with eribulin mesylate. Rats exhibited testicular toxicity (hypocellularity of seminiferous epithelium with hypospermatia/aspermia) following dosing with eribulin mesylate at or above 0.43 times the recommended human dose (mg/m²) given once weekly for 3 weeks, or at or above 0.21 times the recommended human dose (mg/m²) given once weekly for 3 out of 5 weeks, repeated for 6 cycles. Testicular toxicity was also observed in dogs given 0.84 times the recommended human dose (mg/m²) weekly for 5 out of 5 cycles, repeated for 6 cycles.
HOW SUPPLIED/STORAGE AND HANDLING

NDC 62856-389-01
Eribulin mesylate injection, 1 mg/2 mL, in a single-use vial.
One vial per carton.

Store at 25°C (77°F); excursions permitted to 15° – 30°C (59° – 86°F). Do not freeze. Store the vials in their original cartons.

PATIENT COUNSELING INFORMATION

- Advise patients to contact their health care provider for a fever of 100.5°F or greater or other signs or symptoms of infection such as chills, cough, or burning or pain on urination [see Warnings and Precautions (5.1)].

- Advise women of childbearing potential to avoid pregnancy and to use effective contraception during treatment with HALAVEN [see Warnings and Precautions (5.3) and Use in Specific Populations (8.1)].

Distributed by:
Eisai Inc.
Woodcliff Lake, NJ 07677
PATIENT INFORMATION
HALAVEN® (HAL-ih-ven)
(eribulin mesylate) Injection

Read this leaflet before you start receiving HALAVEN and before each injection. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about HALAVEN?
Your healthcare provider should do blood tests regularly to check your blood cell counts before you receive each dose of HALAVEN.

- HALAVEN can cause a decrease in white blood cell count (neutropenia). This can make you more likely to get serious infections that could lead to death. You may need treatment in the hospital with antibiotic medicines.
- Call your healthcare provider right away if you develop any of these symptoms of infection while you are receiving HALAVEN:
  - fever (temperature above 100.5°F)
  - chills
  - cough
  - burning or pain when you urinate.
- HALAVEN can cause numbness, tingling, or burning in your hands and feet (neuropathy). Tell your healthcare provider if you have any of these symptoms.

See “What are possible side effects of HALAVEN?” for more information about side effects.

What is HALAVEN?
HALAVEN is a prescription medicine used to treat people with breast cancer:

- that has spread to other parts of their body, and
- who have already received certain types of anticancer medicines after their breast cancer has spread.

What should I tell my healthcare provider before receiving HALAVEN?
Before you receive HALAVEN, tell your healthcare provider if you:

- have liver or kidney problems.
- have heart problems, including a problem called “congenital long QT syndrome.”
- are pregnant or plan to become pregnant. HALAVEN may harm your unborn baby. Talk with your healthcare provider about birth control methods to prevent pregnancy while you receive HALAVEN. Tell your healthcare provider right away if you become pregnant or think you are pregnant while you are receiving HALAVEN
- are breastfeeding or planning to breastfeed. It is not known if HALAVEN passes into your breast milk. You and your healthcare provider should decide if you will take HALAVEN or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements.

Know the medicines you take. Keep a list of your medicines to show to your healthcare provider and pharmacist when you get a new medicine.

How will I receive HALAVEN?
- HALAVEN is injected directly into your vein.
- HALAVEN is given in “cycles” of treatment, with each cycle lasting 21 days.
- You will receive an injection 1 time each week for two weeks in a row (day 1 and day 8 of a treatment cycle).
- Your healthcare provider may need to decrease your dose of HALAVEN or change how often you receive it, depending on your blood test results.

What are the possible side effects of HALAVEN?
HALAVEN may cause serious side effects, including:

- See “What is the most important information I should know about HALAVEN?”
- HALAVEN can cause changes in your heartbeat (called QTc prolongation). This can cause irregular heartbeats that may lead to death. Your healthcare provider will decide if you need heart monitoring (electrocardiogram or ECG), or blood tests during your treatment with HALAVEN to watch for this problem.

The most common side effects of HALAVEN include:

- weakness or tiredness
- hair loss
- nausea
- constipation

Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the possible side effects of HALAVEN. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about HALAVEN
Medicines are sometimes prescribed for purposes other than those listed in a patient information leaflet. This leaflet summarizes the most important information about HALAVEN. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about HALAVEN that is written for health professionals.

For more information, go to www.HALAVEN.com or call Eisai Inc. at 1-877-873-4724.

What are the ingredients in HALAVEN?
Active Ingredients: eribulin mesylate
Inactive Ingredients: ethanol, water

Distributed by:
Eisai Inc.
Woodcliff Lake, NJ 07677

If you would like a leaflet with larger printing, please contact Eisai Inc. at 1-877-873-4724.

Revised: December 2014

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