HALAVEN® (eribulin mesylate) injection, for intravenous use

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use HALAVEN safely and effectively. See full prescribing information for HALAVEN.

HALAVEN® (eribulin mesylate) injection, for intravenous use
Initial U.S. 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. (1.1)
• Unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen. (1.2)

DOSAGE AND ADMINISTRATION
• Administer 1.4 mg/m2 intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle. (2.1)
• Reduce dose in patients with hepatic impairment or with moderate or severe renal impairment. (2.1)
• Do not mix with other drugs or administer with dextrose-containing solutions. (2.3)

DOSE FORMS AND STRENGTHS
Injection: 1 mg per 2 mL (0.5 mg per mL) (3)

CONTRAINDICATIONS
None (4)

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1.2 Liposarcoma

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2.2 Dose Modification
2.3 Instructions for Preparation and Administration

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

Revised: 02/2021

WARNINGs and PRECAUTIONs
• Neutropenia: Monitor peripheral blood cell counts and adjust dose as appropriate. (5.1)
• Peripheral Neuropathy: Monitor for signs of neuropathy. Manage with dose delay and adjustment. (5.2)
• Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to the fetus and to use effective contraception. (5.3, 8.1, 8.3)
• QT Prolongation: Monitor for prolonged QT intervals in patients with congestive heart failure, bradyarrhythmias, drugs known to prolong the QT interval, and electrolyte abnormalities. Avoid in patients with congenital long QT syndrome. (5.4)

ADVERSE REACTIONS
The most common adverse reactions (≥25%) in metastatic breast cancer were neutropenia, anemia, asthenia/tiredness, alopecia, peripheral neuropathy, nausea, and constipation. (6.1)

The most common adverse reactions (≥25%) in liposarcoma and leiomyosarcoma were fatigue, nausea, alopecia, constipation, peripheral neuropathy, abdominal pain, and pyrexia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eisai Inc. at (1-877-873-4724) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

US320624 REV 6/21
WARNINGS AND PRECAUTIONS

5.1 Neutropenia

In Study 1, seven neutropenias (ANC < 500/mm³) lasting more than one week occurred in 12% (8/503) of patients with metastatic breast cancer, leading to discontinuation in <1% of patients. Febrile neutropenia (fever ≥ 38.5°C with Grade 3 or 4 neutropenia) occurred in 5% (23/503) of patients; two patients (0.4%) died from complications of febrile neutropenia [see Adverse Reactions (6.1)].

In Study 2, seven neutropenias (ANC < 500/mm³) lasting more than one week occurred in 12% (26/222) of patients with liposarcoma or leiomyosarcoma. Febrile neutropenia occurred in 0.9% of patients treated with HALAVEN and fatal neutropenic sepsis in 0% [see Adverse Reactions (6.1)]. 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 (2.2)]. Clinical studies of HALAVEN did not include patients with baseline neutrophil counts below 1500/mm³.

5.2 Peripheral Neuropathy

In Study 1, Grade 3 peripheral neuropathy occurred in 8% (40/503) of patients, and Grade 4 in 0.4% (2/503) of patients with metastatic breast cancer (MBC). Peripheral neuropathy was the most common toxicity leading to discontinuation of HALAVEN (6% of patients; 24/503) in Study 2. Neutropathy lasting more than one year occurred in 5% (26/503) of patients. Twenty-two percent (109/503) of patients developed a new or worsening neuropathy that had not recovered within a median follow-up duration of 254 days (range 25-662 days).

In Study 2, Grade 3 peripheral neuropathy occurred in 3.1% (7/223) of HALAVEN-treated patients. Peripheral neuropathy led to discontinuation of HALAVEN in 0.9% of patients. The median time to first occurrence of peripheral neuropathy of any severity was 5 months (range: 3.5 months to 9 months). Neutropathy lasting more than 60 days occurred in 58% (38/65) of patients. Sixty-three percent (41/65) had not recovered within a median follow-up duration of 6.4 months (range: 27 days to 269 days).

Monitor patients closely for signs of peripheral motor and sensory neuropathy. Withhold HALAVEN in patients who experience Grade 3 or 4 peripheral neuropathy, until resolution to Grade 0 or less [see Dosage and Administration (2.2)].

5.3 Embryo-Fetal Toxicity

Based on findings from an animal reproduction study and its mechanism of action, HALAVEN can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of HALAVEN in pregnant women. Animal reproduction studies, eribulin mesylate caused embryo-fetal toxicity when administered to pregnant rats during organogenesis at doses below the recommended human dose. Advise pregnant women of the potential risk to their pregnancy and advise males with female partners 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 at least 3.5 months following the final dose [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, bradycardia, patients taking medications that can prolong QT interval, including Class I 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.

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 prolongation (see Warnings and Precautions (5.4))

In clinical trials, HALAVEN has been administered to 1963 patients including 467 patients exposed to HALAVEN for 8 months or longer. The majority of the 1963 patients were women (92%) with a median age of 55 years (range: 17 to 85 years). The racial and ethnic distribution was White (72%), Black (4%), Asian (9%), and other (3%).

Metastatic Breast Cancer

The most common adverse reactions (≥25%) reported in patients receiving HALAVEN were neutropenia, anemia, asthenia/fatigue, alopecia, peripheral neuropathy, nausea, and constipation. The most common serious adverse reactions reported in patients receiving HALAVEN were febrile neutropenia (≥5%) and neutropenia (≥5%). The most common adverse reaction resulting in discontinuation of HALAVEN was peripheral neuropathy (5%).

The adverse reactions described in Table 2 were identified in 750 patients treated in Study 1 (see Clinical Studies (14.1)). 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 dacarbazine at doses of 850 mg/m² (20%), 1000 mg/m² (64%), or 1200 mg/m² (16%) every 3 weeks. A total of 223 patients received HALAVEN and 221 patients received dacarbazine. Patients were required to have received at least two prior systemic chemotherapy regimens and 76% of patients were neutropenic. Patients enrolled in Study 1 already had pre-existing Grade 1 peripheral neuropathy, known central nervous system metastasis, elevated serum bilirubin or significant chronic liver disease, history of myocardial infarction within 6 months, history of New York Heart Association Class II or IV heart failure, or cardiac arrhythmia requiring treatment. The median age of the safety population in Study 2 was 56 years (range: 24 to 83 years); 67% female; 73% White, 3% Black or African American, 8% Asian/Pacific Islander, and 15% unknown; 99% received prior anthracycline-containing regimen; and 99% received ≥2 prior regimens. The median duration of exposure was 2.3 months (range: 21 days to 26 months) for patients receiving HALAVEN (see Clinical Studies (14.2)).
The most common adverse reactions (≥25%) reported in patients receiving HALAVEN were fatigue, nausea, alopecia, constipation, peripheral neuropathy, abdominal pain, and pruritus. The most common (≥5%) Grade 3-4 laboratory abnormalities reported in patients receiving HALAVEN were neutropenia, hyponatremia, and hypocalcemia. The most common serious adverse reactions reported in patients receiving HALAVEN were neutropenia (4.9%) and pruynx (4.5%). Permanent discontinuation of HALAVEN for adverse reactions occurred in 8% of patients. The most common adverse reactions resulting in discontinuation of HALAVEN were fatigue and thrombocytopenia (0.9% each). Twenty-six percent of patients required at least one dose reduction. The most frequent adverse reactions that led to dose reduction were neutropenia (18%) and peripheral neuropathy (4%). Table 3 summarizes the incidence of adverse reactions occurring in at least 10% of patients in the HALAVEN-treated arm in Study 2.

### Table 3: Adverse Reactions occurring in ≥10% (all Grades) of Patients Treated on the HALAVEN arm and at a Higher Incidence Than in the Dacarbazine Arm (Between Arm Difference of ≥5% for All Grades or ≥2% for Grades 3 and 4) (Study 2)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>HALAVEN n=223</th>
<th>Dacarbazine n=221</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral Neuropathy</td>
<td>23%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Headache</td>
<td>18%</td>
<td>0%</td>
</tr>
<tr>
<td>General disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>28%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>32%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Abdominal pain†</td>
<td>20%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>14%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>35%</td>
<td>NA*</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>11%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Infectious</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other clinically important adverse reactions occurring in ≥10% of the HALAVEN-treated patients were:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Gastrointestinal Disorders: nausea (41%); vomiting (13%); diarrhea (17%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• General Disorders: asthaenia/fatigue (62%); peripheral edema (12%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Metabolism and Nutrition Disorders: decreased appetite (19%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Musculoskeletal and Connective Tissue Disorders: arthralgia/myalgia (16%); back pain (16%); Respiratory Disorders: cough (18%); Less Common Adverse Reactions: The following additional clinically important adverse reactions were reported in ≥5% to &lt;10% of the HALAVEN-treated group:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Blood and Lymphatic System Disorders: thrombocytopenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Eye Disorders: increased lacrimation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Gastrointestinal Disorders: dyspepsia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Metabolism and Nutrition Disorders: hyperglycemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Musculoskeletal and Connective Tissue Disorders: muscle spasms, musculoskeletal pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Nervous System Disorders: dizziness, dyseusia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Psychiatric Disorders: insomnia, anxiety</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Respiratory, Thoracic, and Mediastinal Disorders: orphangeal pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Vascular Disorders: hypotension</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4: Laboratory Abnormalities occurring in ≥10% (all Grades) of Patients Treated on the HALAVEN arm and at a Higher Incidence Than in the Dacarbazine Arm (Between Arm Difference of ≥5% for All Grades or ≥2% for Grades 3 and 4) (Study 2)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>HALAVEN</th>
<th>Dacarbazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td>All Grades</td>
<td>Grades 3-4</td>
</tr>
<tr>
<td>Anemia</td>
<td>70%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>63%</td>
<td>32%</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased alanineaminotransf.</td>
<td>43%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Increased aspartateaminotransf.</td>
<td>36%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>30%</td>
<td>5.4%</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>28%</td>
<td>5%</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>20%</td>
<td>3.2%</td>
</tr>
</tbody>
</table>

Each test incidence is based on the number of patients who had both baseline and at least one on-study measurement, and at least 1 grade increase from baseline. Halaven group (range 221-222) and dacarbazine group (range 214-215). Laboratory results were graded per NCI CTCAE v4.03.

### 6.2 Postmarketing Experience

The following adverse drug reactions have been identified during post-approval of HALAVEN. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- **Blood and Lymphatic System Disorders:** lymphopenia
- **Gastrointestinal Disorders:** pancreatitis
- **Hepatobiliary Disorders:** hepatotoxicity
- **Immune System Disorders:** drug hypersensitivity
- **Infections and Infestations:** pneumonia, sepsis/neutropenic sepsis
- **Metabolism and Nutrition Disorders:** hypoglycemia, dehydratation
- **Respiratory, thoracic and mediastinal disorders:** interstitial lung disease
- **Skin and Subcutaneous Tissue Disorders:** pruritus, Stevens-Johnson syndrome, toxic epidermal necrolysis

### 7 DRUG INTERACTIONS

#### 7.1 Effects of Other Drugs on HALAVEN

No drug-drug interactions are expected with CYP3A4 inhibitors, CYP3A4 inducers or F-glycoprotein (P-gp) inhibitors. Clinically meaningful differences in exposure (AUC) were not observed in patients with advanced solid tumors when HALAVEN was administered with or without ketoconazole (a strong inhibitor of CYP3A4 and a P-gp inhibitor) and when HALAVEN was administered with or without rifampin (a CYP3A4 inducer) [see Clinical Pharmacology (12.3)].

#### 7.2 Effects of HALAVEN on Other Drugs

Eribulin does not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4 enzymes or induce CYP1A2, CYP2C9, CYP2C19 or CYP3A4 enzymes at relevant clinical concentrations. Eribulin is not expected to alter the plasma concentrations of drugs that are substrates of these enzymes [see Clinical Pharmacology (12.3)].

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

**Risk Summary**

Based on findings from an animal reproduction study and its mechanism of action, HALAVEN can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1)]. There are no available data on the use of HALAVEN during pregnancy. In an animal reproduction study, eribulin mesylate caused embryo-fetal toxicity when administered to pregnant rats during organogenesis at doses below the recommended human dose [see Data].

Advising pregnant women of the potential risk to a fetus. The estimated background risks of major birth defects and miscarriage for the indicated populations are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically-recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

**Data**

**Animal Data**

In an embryo-fetal developmental toxicity study, pregnant rats received intravenous infusion of eribulin mesylate during organogenesis (Gestation Days 8, 10, and 12) at doses approximately 0.9, 0.13, 0.43 and 0.64 times the recommended human dose, based on body surface area. Increased abortion and severe fetal external or soft tissue malformations, including the absence of a lower jaw and tongue, or stomach and spleen, were observed at doses 0.64 times the recommended human dose of 1.4 mg/m² based on body surface area. Increased embryo-fetal death/resorption, reduced fetal weights, and minor skeletal abnormalities consistent with developmental delay were also reported at doses at or above a maternally toxic dose of approximately 0.43 times the recommended human dose.

#### 8.2 Lactation

**Risk Summary**

There is no information regarding the presence of eribulin mesylate or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. No lactation studies in animals were conducted. 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.

#### 8.3 Females and Males of Reproductive Potential

**Contraception**

Based on findings from an animal reproduction study and its mechanism of action, HALAVEN can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)].

**Advising males with female partners of reproductive potential to use effective contraception during treatment with HALAVEN and for at least 2 weeks following the final dose.**

### 8.4 Pediatric Use

**The safety and effectiveness of HALAVEN in pediatric patients below the age of 18 years have not been established.**

#### 8.5 Geriatric Use

Study 1 did not include sufficient numbers of subjects with metastatic breast cancer aged 65 years and older to determine whether they respond differently from younger subjects. Of the 827 subjects who received the recommended dose and schedule of HALAVEN in clinical studies with advanced breast cancer, 15% (121/827) were 65 and older, and 2% (17/827) patients were 75 and older. No overall differences in safety were observed between these subjects and younger subjects.

Clinical studies of HALAVEN did not include a sufficient number of subjects in Study 2 aged 65 years and older to determine whether they respond differently from younger subjects.

#### 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 of 0.7 mg/m² is recommended for patients with moderate hepatic impairment.
improvement (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 (CLcr 15-49 mL/min), reduce the starting dose to 1.1 mg/m² [see Dosage and Administration (2.1), Clinical Pharmacology (12.2)].

10 OVERDOSAGE
Overdose 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 contains eribulin mesylate, a microtubule dynamics inhibitor. Eribulin mesylate is a synthetic analogue of halichondrin B, a product isolated from the marine sponge Halichondria okadaï. The chemical name for eribulin mesylate is 11,15:18,21:24,28-Triepoxy-7,9-ethano-

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 antimitotic mechanism leading to G₂/M cell-cycle block, disruption of mitotic spindles, and, ultimately, apoptotic cell death after prolonged mitotic blockage.

In addition, eribulin treatment of human breast cancer cells caused changes in morphology and gene expression as well as decreased migration and invasiveness in vitro. In mouse xenograft models of human breast cancer, eribulin 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.

12.2 Pharmacokinetics
Carcin Electrochemistry
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 9, with no prolongation observed on Day 1. The maximum mean QTc change from baseline (95% upper confidence interval) was 11.4 (19.5) ms.

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 1.16 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.

Elimination
Metabolism
Unchanged eribulin was the major circulating species in plasma following administration of

Table 5: Comparison of Overall Survival in HALAVEN and Control Arm - Study 1

<table>
<thead>
<tr>
<th>Overall Survival</th>
<th>HALAVEN (n=396)</th>
<th>Control Arm (n=392)</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></td>
</tr>
</tbody>
</table>

Updated survival analysis
Number of deaths 386 203
Median, months (95% CI) 13.2 (12.1, 14.4) 10.6 (9.2, 12.0)

CI = confidence interval
Based on Cox proportional hazards model stratified by geographic region, HER2 status, and prior capcitabine therapy.
Based on a log-rank test stratified by geographic region, HER2 status, and prior capcitabine therapy.
14.2 Liposarcoma

The efficacy and safety of HALAVEN were evaluated in Study 2, an open-label, randomized (1:1), multicenter, active-controlled trial. Eligible patients were required to have unresectable, locally advanced or metastatic liposarcoma or leiomyosarcoma, at least two prior systemic chemotherapies (one of which must have included an anthracycline), and disease progression within 6 months of the most recent chemotherapy regimen. Patients were randomized to HALAVEN 1.4 mg/m² administered intravenously on Days 1 and 8 of a 21-day cycle or to dacarbazine at a dose of 850 mg/m², 1000 mg/m², or 1200 mg/m² administered intravenously every 21 days (dacarbazine dose was selected by the investigator prior to randomization). Treatment continued until disease progression or unacceptable toxicity. Randomization was stratified by histology (liposarcoma or leiomyosarcoma), number of prior therapies (2 vs. > 2), and geographic region (U.S. and Canada vs. Western Europe, Australia, and Israel vs. Eastern Europe, Latin America, and Asia). The major efficacy outcome measure was overall survival (OS). Additional efficacy outcome measures were progression-free survival (PFS) and confirmed objective response rate (ORR) as assessed by the investigator according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1).

Table 6: Efficacy Results for the Liposarcoma Stratum and All Patients* in Study 2

<table>
<thead>
<tr>
<th>Liposarcoma Stratum</th>
<th>All Patients*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halaven (n=71)</td>
<td>Dacarbazine (n=72)</td>
</tr>
<tr>
<td>Overall Survival</td>
<td></td>
</tr>
<tr>
<td>Deaths, n (%)</td>
<td>52 (73)</td>
</tr>
<tr>
<td>Median, months (95% CI)</td>
<td>15.6 (10.2, 18.6)</td>
</tr>
<tr>
<td>Hazard ratio (HR) (95% CI)</td>
<td>0.51 (0.35, 0.75)</td>
</tr>
</tbody>
</table>

Progression-free survival

| Events, n (%) | 57 (80) | 59 (82) | 194 (86) | 185 (84) |
| Disease progression | 53 | 57 | 180 | 170 |
| Death | 4 | 7 | 14 | 15 |
| Median, months (95% CI) | 2.9 (1.6, 4.8) | 1.7 (1.4, 2.6) | 2.6 (2.0, 2.8) | 2.6 (1.7, 2.7) |
| HR (95% CI) | 0.52 (0.35, 0.78) | 0.86 (0.69, 1.06) |

Objective response rate (% (95% CI))

| Objective response rate | 1.4 (0.7, 7.8) | 0 (0.4, 2.4) | 4.0 (1.8, 7.5) | 5.0 (2.5, 8.7) |

* Efficacy data from one study site enrolling six patients were excluded.
* All patients = liposarcoma and leiomyosarcoma.
* N/A = not applicable

16 HOW SUPPLIED/STORAGE AND HANDLING

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Printed in USA / 03/2021
HALAVEN® (HAL-ih-ven) (eribulin mesylate) injection, for intravenous use

**What is the most important information I should know about HALAVEN?**

HALAVEN can cause serious side effects, including:

- **Low white blood cell count (neutropenia).** This can lead to serious infections that could lead to death. Your healthcare provider will check your blood cell counts before you receive each dose of HALAVEN and during treatment. Call your healthcare provider right away if you develop any of these symptoms of infection:
  - fever (temperature above 100.5°F)
  - chills
  - cough
  - burning or pain when you urinate

- **Numbness, tingling, or pain in your hands or feet (peripheral neuropathy).** Peripheral neuropathy is common with HALAVEN and sometimes can be severe. Tell your healthcare provider if you have new or worsening symptoms of peripheral neuropathy.

- Your healthcare provider may delay, decrease your dose, or stop treatment with HALAVEN if you have side effects.

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 the body, and
  - who have already received certain types of anticancer medicines after the cancer has spread

- **Liposarcoma**
  - that cannot be treated with surgery or has spread to other parts of the body, and
  - who have received treatment with a certain type of anticancer medicine

It is not known if HALAVEN is safe and effective in children under 18 years of age.

**Before you receive HALAVEN, tell your healthcare provider about all of your medical conditions, including if you:**

- have liver or kidney problems
- have heart problems, including a problem called congenital long QT syndrome
- have low potassium or low magnesium in your blood
- are pregnant or plan to become pregnant. HALAVEN can harm your unborn baby. Tell your healthcare provider right away if you become pregnant or think you are pregnant during treatment with HALAVEN.
  - **Females** who are able to become pregnant should use an effective birth control method before you start treatment with HALAVEN and for at least 2 years after the final dose of HALAVEN.
  - **Males** should use an effective form of birth control when having sex with female partners who are able to become pregnant during treatment with HALAVEN and for 3 1/2 months (14 weeks) after the final dose of HALAVEN.
- are breastfeeding or plan to breastfeed. It is not known if HALAVEN passes into your breast milk. Do not breastfeed during treatment with HALAVEN and for 2 weeks after the final dose of HALAVEN.

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

**How will I receive HALAVEN?**

- HALAVEN is given by intravenous (IV) injection in your vein.
- HALAVEN is given in “cycles” of treatment, with each cycle lasting 21 days.
- HALAVEN is usually given on day 1 and day 8 of a treatment cycle.

**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 QT prolongation).** This can cause irregular heartbeats. Your healthcare provider may do heart monitoring (electrocardiogram or ECG) or blood tests during your treatment with HALAVEN to check for heart problems.

The most common side effects of HALAVEN in people with breast cancer include:

- low white blood cell count (neutropenia)
- low red blood cell count (anemia)
- weakness or tiredness
- hair loss (alopecia)
- nausea
- constipation

The most common side effects of HALAVEN in people with liposarcoma include:

- tiredness
- nausea
- hair loss (alopecia)
- constipation
- stomach pain
- fever

Your healthcare provider will do blood tests before and during treatment while you are taking HALAVEN. The most common changes to blood tests in people with liposarcoma include:

- low white blood cell count (neutropenia)
- decreased blood levels of potassium or calcium

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. 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. You can ask your pharmacist or healthcare provider for information about HALAVEN that is written for health professionals.

**What are the ingredients in HALAVEN?**

**Active Ingredient:** eribulin mesylate

**Inactive Ingredients:** dehydrated alcohol, water for injection, and sodium hydroxide or hydrochloric acid may be used for pH adjustment.

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For more information, go to www.HALAVEN.com or call Eisai Inc. at 1-877-873-4724. If you would like a leaflet with larger printing, please contact Eisai Inc. at 1-877-873-4724.

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