HALAVEN® (eribulin mesylate) injection, for intravenous use

Initial U.S. Approval: 2010

RECENT MAJOR CHANGES

Indications and Usage (1.2) 01/2016

Warnings and Precautions (5.1, 5.2, 5.3) 01/2016

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)

WARNINGS AND PRECAUTIONS

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

To report SUSPECTED ADVERSE REACTIONS, contact Eisai Inc. at (1-877-873-4724) or FDA at 1-888-FDA-1088 or www.fda.gov/medwatch

USE IN SPECIFIC POPULATIONS

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

8.3 Females and Males of Reproductive Potential

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Hepatic Impairment

8.7 Renal Impairment

OVERDOSAGE

10 OVERDOSAGE

11 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

14.1 Metastatic Breast Cancer

14.2 Liposarcoma

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

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>
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<tbody>
<tr>
<td>Permanently reduce the 1.4 mg/m² HALAVEN dose for any of the following:</td>
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<tr>
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ANC - absolute neutrophil count

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

8.3 Females and Males of Reproductive Potential

- Use effective contraception during treatment with HALAVEN and for 3 1/2 months after stopping treatment.

8.4 Pediatric Use

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

8.5 Geriatric Use

In Study 1, severe neutropenia (ANC < 500/mm³) lasting more than one week occurred in 12% of patients, and Grade 4 neutropenia occurred in 5% of patients. (8/503) of patients developed Grade 3 peripheral motor neuropathy.

8.6 Hepatic Impairment

The recommended dose of HALAVEN in patients with moderate or severe renal impairment

- The Day 8 dose may be delayed for a maximum of 1 week.

8.7 Renal Impairment

In an uncontrolled open-label ECG study in 26 patients, QT prolongation was observed on study, treatment, and at least 1 grade increase from baseline. Halaven group (range: 476.6-904.4 ms vs. 462.9-561.9 ms).

8.5 Geriatric Use

Based on findings from an animal reproduction study and its mechanism of action, HALAVEN is contraindicated in females of reproductive potential during treatment and for 3 1/2 months after stopping treatment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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Reduce dose in patients with hepatic impairment or with moderate or severe renal impairment. (2.1)

Indications and Usage (1.2) 01/2016

FULL PRESCRIBING INFORMATION

6.2 Postmarketing Experience

6.1 Clinical Trials Experience

5.3 Embryo-Fetal Toxicity

5.2 Peripheral Neuropathy

2.2 Dose Modification

[see Clinical Studies (14.2)]

who have received a prior anthracycline-containing regimen

1.2 Liposarcoma

disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant

The recommended dose of HALAVEN in patients with mild hepatic impairment (Child-Pugh A) is

The Day 8 dose may be delayed for a maximum of 1 week.

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 6 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 (≥2%) and neutropenic fever (≥2%).

The most common (≥5%) Grade 3-4 laboratory abnormalities reported in patients receiving HALAVEN and during treatment. Call your healthcare provider right away if you get any of these symptoms.

The mean time to recovery from severe neutropenia (<500/mm3) was 8 days. Grade 3 or greater thrombocytopenia occurred in 1% (7/503) 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. Patients treated with HALAVEN and fatal neutropenic sepsis in 0.9% (26/222) of patients with liposarcoma or leiomyosarcoma. Febrile neutropenia occurred in 0.9% of patients treated with HALAVEN and fatal neutropenic sepsis in 0.9% (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 1,500/mm3.

5.3 Embryo-Fetal Toxicity

HALAVEN in patients who experience Grade 3 or 4 peripheral neuropathy, until resolution to Grade 2 or less (see Dosage and Administration (2.2)).

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. In animal reproduction studies, embulbin 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 a fetus. 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 at least 3.5 months following the final dose (see Use in Specific Populations (8.1)).

4.7 QT Prolongation

In an uncontrolled open-label ECG study in 26 patients, QT prolongation was observed on Day 8, independent of embulbin 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 prolongation (see Warnings and Precautions (5.4))

In clinical trials, HALAVEN has been administered to 1963 patients including 467 patients exposed to HALAVEN for 6 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%).
The most common adverse reactions (≥25%) reported in patients receiving HALAVEN were fatigue, nausea, alopecia, constipation, peripheral neuropathy, abdominal pain, and pyrexia. The most common (≥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%). Permanence 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>29%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>18%</td>
<td>0%</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>29%</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>Headache</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Other clinically important adverse reactions occurring in ≥10% of the HALAVEN-treated patients were:  
- Gastrointestinal Disorders: nausea (41%), vomiting (13%), diarrhea (17%)  
- General Disorders: asthenia/fatigue (62%); peripheral edema (12%)  
- Metabolism and Nutrition Disorders: decreased appetite (19%)  
- Musculoskeletal and Connective Tissue Disorders: arthralgia/myalgia (16%); back pain (16%)  
- Respiratory Disorders: cough (18%)  
| Less Common Adverse Reactions: The following additionally clinically important adverse reactions were reported in ≥5% to <10% of the HALAVEN-treated group:  
- Blood and Lymphatic System Disorders: thrombocytopenia  
- Eye Disorders: increased lacrimation  
- Gastrointestinal Disorders: dyspepsia  
- Metabolism and Nutrition Disorders: hyperglycemia  
- Musculoskeletal and Connective Tissue Disorders: muscle spasm, musculoskeletal pain  
- Nervous System Disorders: dizziness, dysequisia  
- Psychiatric Disorders: insomnia, anxiety  
- Respiratory, Thoracic, and Mediastinal Disorders: ophthalmalgia pain  
- Vascular Disorders: hypotension

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 All Grades</th>
<th>Grades 3-4</th>
<th>Dacarbazine All Grades</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>70%</td>
<td>4.1%</td>
<td>52%</td>
<td>6%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>63%</td>
<td>32%</td>
<td>30%</td>
<td>8.9%</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased alanine aminotransferase [ALT]</td>
<td>43%</td>
<td>2.3%</td>
<td>28%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase [AST]</td>
<td>36%</td>
<td>0.9%</td>
<td>16%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>30%</td>
<td>5.4%</td>
<td>14%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>28%</td>
<td>5%</td>
<td>18%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>20%</td>
<td>3.2%</td>
<td>11%</td>
<td>1.4%</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 214-216)

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: hepatoxicity
- Immune System Disorders: drug hypersensitivity
- Infections and Infestations: pneumonia, sepsis/neutropenic sepsis
- Metabolism and Nutrition Disorders: hypomagnesemia, dehydration
- 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 P-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 ritampin (a CYP3A4 inducer) [see Clinical Pharmacology (12.3)].

7.2 Effect of HALAVEN on Other Drugs Erubulin does not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4 enzymes or induce CYP1A2, CYP2C9, CYP2C19 or CYP3A4 enzymes at relevant clinical concentrations. Erubulin 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 (11.2)]. There are no available data on the use of HALAVEN during pregnancy. In an animal reproduction study, erubulin caused embryo-fetal toxicity when administered to pregnant rats during organogenesis at doses below the recommended human dose [see Data]. Advise 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.

8.2 Lactation Risk Summary There is no information regarding the presence of erubulin 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 erubulin 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 Females 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)]. Advise females of reproductive potential to use effective contraception during treatment with HALAVEN and for at least 2 weeks following the final dose. Males Based on its mechanism of action, 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.

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 527 subjects who received the recommended dose and schedule of HALAVEN in clinical studies with metastatic breast cancer, 15% (71/527) were 65 and older, and 2% (11/527) 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 Hematopic Impairment Administration of HALAVEN at a dose of 1.1 mg/m² to patients with mild hematopic impairment and 0.7 mg/m² to patients with moderate hematopic impairment resulted in similar exposure to erubulin as a dose of 1.4 mg/m² to patients with normal hematopic function. Therefore, a lower starting dose of 1.1 mg/m² is recommended for patients with mild hematopic impairment (Child-Pugh A) and 0.7 mg/m² is recommended for patients with moderate hematopic impairment.
HALAVEN® is a registered trademark used by Eisai Inc. under license from for information about HALAVEN that is written for health professionals.

General information about HALAVEN at 1-800-FDA-1088.

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

- low white blood cell count (neutropenia)
- increase in lactic acid
- increase in liver enzymes
- mild kidney impairment (Child-Pugh B). HALAVEN was not studied in patients with severe hepatic impairment (Child-Pugh C).

7.3 Adverse Drug Reactions

7.3.1 Hematological Abnormalities

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

- nausea
- vomiting
- anorexia
- fatigue
- constipation
- diarrhea
- stomatitis
- decreased appetite

7.4 Immune System Disorders:

In an embryo-fetal developmental toxicity study, pregnant rats received intravenous infusion of and miscarriage in clinically-recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

7.5 Hepatobiliary Disorders:

Based on its mechanism of action, advise males with female partners of reproductive potential to use a contraceptive method with high failure rates, or surgically sterilized males during treatment with HALAVEN.

9.1 Pregnancy

In an embryo-fetal developmental toxicity study, eribulin mesylate caused embryo-fetal toxicity when administered to pregnant rats during organogenesis at doses below the recommended human dose and at or above 0.21 times the recommended human dose.

10.12 Prolonged QT Interval

The effect of HALAVEN on the QTc interval was assessed in an open-label, uncontrolled, single-center, 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 QTc change from baseline (95% upper confidence interval) was 11.4 (12.0) ms.

10.13 CYP450 Interactions

Eribulin is a substrate of anion transporting polypeptides (OATP1B1, OATP1B3), organic anion transporters (OAT1, OAT3), organic cation transporters (OCT1, OCT2), and multidrug and toxin extrusion (MATE1).

13. NONCLINICAL TOXICITY

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.

Fertility studies have not been conducted with eribulin mesylate in humans or animals; however, nonclinical findings in repeat-dose dog and rat toxicology studies suggest that male fertility may be contraindicated by treatment with eribulin mesylate. Rare sex-related fetal abnormalities were also observed in dogs given 0.84 times the recommended human dose that are substrates of these enzymes and it is unlikely that eribulin will affect plasma levels of drugs that are substrates of CYP enzymes.

14.1 Metastatic Breast Cancer

Study 1 was an open-label, randomized, multicenter trial of 762 patients with metastatic breast cancer who had not received prior chemotherapy. Patients were randomized to receive HALAVEN (n=386) or a single-agent therapy selected prior to randomization (control arm, n=376). 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.

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: 6.6%, 14.3%) and the median response duration was 4.8 months (95% CI: 3.9, 5.3 months).

<table>
<thead>
<tr>
<th>Table 5: Comparison of Overall Survival in HALAVEN and 10</th>
<th>Overall Survival</th>
<th>HALAVEN (n=386)</th>
<th>Control Arm (n=376)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary survival analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of deaths</td>
<td>274</td>
<td>148</td>
<td></td>
</tr>
<tr>
<td>Median, months (95% CI)</td>
<td>13.1 (11.6, 14.3)</td>
<td>10.6 (9.3, 12.5)</td>
<td></td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>0.81 (0.66, 0.99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Updated survival analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of deaths</td>
<td>386</td>
<td>203</td>
<td></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>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval

a Based on Cox proportional hazards model stratified by geographic region, HER2 status, and prior capecitabine therapy.

b Based on a log-rank test stratified by geographic region, HER2 status, and prior capecitabine therapy.

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 (5:3).

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 Pharmacodynamics

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 9, with no prolongation observed on Day 1. The maximum QTc change from baseline (95% upper confidence interval) was 11.4 (12.0) 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 1.6 L/h/m² to 2.42 L/h/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 40% to 60%. 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 40 mg/m² eribulin mesylate. In vitro metabolism of eribulin was negligible in vitro.

Excretion

Eribulin is eliminated primarily in feces unchanged. After administration of [14C]-eribulin to patients, approximately 82% of the dose was eliminated in feces and 3% in urine. Unchanged eribulin accounted for approximately 80% and 91% of total eribulin in feces and urine, respectively.

Specific Populations

Age, Sex, and Race/Ethnicity: Based on a population pharmacokinetic analysis with data collected from 340 patients, sex, race, and age do not have a clinically meaningful effect on the exposure of eribulin.

Hepatic Impairment

In a study evaluating the effect of hepatic impairment on the PK of eribulin, eribulin exposures increased by 1.8-fold in patients with mild hepatic impairment (Child-Pugh A; n=7) and by 2.5-fold in patients with moderate (Child-Pugh B; n=6) hepatic impairment as compared to patients with normal hepatic function (n=8). 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 at a dose of 1.4 mg/m² to patients with normal hepatic function.
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). Patients in the dacarbazine arm were not offered HALAVEN at the time of disease progression. A total of 446 patients were randomized, 225 to the HALAVEN arm and 221 to the dacarbazine arm. The median age was 56 years (range: 24 to 83); 33% were male; 73% were White; 44% had ECOG performance status 0, 53% had ECOG PS of 1; 68% had leiomyosarcoma and 32% had liposarcoma; 39% were enrolled in U.S. and Canada (Regional 1) and 40% were enrolled in Western Europe, Australia, and Israel (Regional 2); and 47% received more than two prior systemic chemotherapies. The most common (≥40%) prior systemic chemotherapies were doxorubicin (90%), ifosfamide (82%), gemcitabine (59%), trabectedin (50%), and docetaxel (48%). Of the 143 patients with liposarcoma, the median age was 55 years (range: 32 to 62); 62% were male, 72% were White; 41% had ECOG PS of 0 and 53% had ECOG PS of 1; 35% were enrolled in Regional 1 and 51% were enrolled in Regional 2, and 44% received more than two prior systemic chemotherapies. The distribution of subtypes of liposarcoma, based on local histologic assessment, were 45% dedifferentiated, 37% myxoid/round cell, and 18% pleomorphic. Study 2 demonstrated a statistically significant improvement in OS in patients randomized to HALAVEN compared with dacarbazine (see Table 6). There was no significant difference in progression-free survival in the overall population. Treatment effects of HALAVEN were limited to patients with liposarcoma based on pre-planned, exploratory subgroup analyses of OS and PFS (see Tables 6 and 7 and Figure 2). There was no evidence of efficacy of HALAVEN in patients with advanced or metastatic leiomyosarcoma in Study 2 (see Table 7).
HALAVEN® (HAL-ih-ven)
(erebulin 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 during treatment with HALAVEN and for at least 2 weeks 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)  • hair loss (alopecia)
• low red blood cell count (anemia)  • nausea
• weakness or tiredness  • constipation

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

• tiredness  • constipation
• nausea  • stomach pain
• hair loss (alopecia)  • 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: ethanol, water

HALAVEN® is a registered trademark used by Eisai Inc. under license from Eisai R&D Management Co., Ltd.
Distributed by:
Eisai Inc.
Woodcliff Lake, NJ 07677

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.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 01/2016

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