Halaven® (eribulin mesylate) Injection | 0.5 mg/mL

SAFETY & DOSING GUIDE

Indication

Metastatic Breast Cancer

HALAVEN (eribulin mesylate) Injection is indicated for the treatment of patients with metastatic breast cancer (mBC) who have previously received at least 2 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.

Selected Safety Information

Warnings and Precautions

Neutropenia: Severe neutropenia (ANC <500/mm^3) lasting >1 week occurred in 12% of patients with mBC. Febrile neutropenia occurred in 5% of patients with mBC and 2 patients (0.4%) died from complications. Patients with mBC with elevated liver enzymes >3 x ULN and bilirubin >1.5 x ULN experienced a higher incidence of Grade 4 neutropenia and febrile neutropenia than patients with normal levels. Monitor complete blood cell counts prior to each dose, and increase the frequency of monitoring in patients who develop Grade 3 or 4 cytopenias. Delay administration and reduce subsequent doses in patients who experience febrile neutropenia or Grade 4 neutropenia lasting >7 days.

Please see all Selected Safety Information throughout and full Prescribing Information.

Monitor adverse reactions (ARs) that may occur with HALAVEN®

A PLAN FOR AR MANAGEMENT

ESTABLISH
baseline ARs

EVALUATE
ARs during treatment[1]

MANAGE
accordingly with recommended dosing schedule and modifications[1]

EMBRACE: A PHASE III, RANDOMIZED, OPEN-LABEL, MULTICENTER, MULTINATIONAL TRIAL[1,2]

- From the Phase III, randomized (2:1), open-label, multicenter, multinational Eisai Metastatic Breast Cancer Study Assessing Physician's Choice versus E7389 (Eribulin) (EMBRACE) trial of HALAVEN administered at a dose of 1.4 mg/m^2 IV for 2 to 5 minutes on Days 1 and 8 of a 21-day cycle (n=508) vs TPC in patients with mBC (n=254). Primary endpoint was overall survival (OS).[1,2]
- Therapies in the TPC arm consisted of 97% chemotherapy (26% vinorelbine, 18% gemcitabine, 18% capecitabine, 16% taxanes [including paclitaxel, docetaxel, nab-paclitaxel, and ixabepilone], 9% anthracyclines, and 10% other chemotherapy) and 3% hormone therapy.[1,2]

AR=adverse reaction; mBC=metastatic breast cancer; TPC=Treatment of Physician's Choice.

Selected Safety Information

Warnings and Precautions (cont'd)

Peripheral Neuropathy: Grade 3 peripheral neuropathy occurred in 8% of patients with mBC (Grade 4=0.4%) and 22% developed a new or worsening neuropathy that had not recovered within a median follow-up duration of 269 days (range 25-662 days). Neuropathy lasting >1 year occurred in 5% of patients with mBC. Patients should be monitored for signs of peripheral motor and sensory neuropathy. Withhold HALAVEN in patients who experience Grade 3 or 4 peripheral neuropathy until resolution to Grade 2 or less.

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Safety Profile Demonstrated in the Phase III EMBRACE trial

ADVERSE REACTIONS[1]

		HALAVEN® (n=503)		TPC (n=247)	
INCIDENCE ≥10% BY GRADE[a]		**All**	**≥3**	**All**	**≥3**
Blood and lymphatic system disorders[b]	Neutropenia	82%	57%	53%	23%
	Anemia	58%	2%	55%	4%
Nervous system disorders	Peripheral neuropathy[c]	35%	8%	16%	2%
	Headache	19%	<1%	12%	<1%
General disorders	Asthenia/fatigue	54%	10%	40%	11%
	Pyrexia	21%	<1%	13%	<1%
	Mucosal inflammation	9%	1%	10%	2%
Gastrointestinal disorders	Nausea	35%	1%	28%	3%
	Constipation	25%	1%	21%	1%
	Vomiting	18%	1%	18%	1%
	Diarrhea	18%	0%	18%	0%
Musculoskeletal and connective tissue disorders	Arthralgia/myalgia	22%	<1%	12%	1%
	Back pain	16%	1%	7%	2%
	Bone pain	12%	2%	9%	2%
	Pain in extremity	11%	1%	10%	1%
Metabolism and nutrition disorders	Decreased weight	21%	1%	14%	<1%
	Anorexia	20%	1%	13%	1%
Respiratory, thoracic, and mediastinal disorders	Dyspnea	16%	4%	13%	4%
	Cough	14%	0%	9%	0%
Skin and subcutaneous tissue disorders	Alopecia	45%	NA[d]	10%	NA[d]
Infections	Urinary tract infection	10%	1%	5%	0%

OF THE PATIENTS RECEIVING HALAVEN:

87%

DID **NOT** HAVE **ADVERSE EVENTS LEADING TO DISCONTINUATION**[2]

- 13% of patients receiving HALAVEN had adverse events leading to discontinuation vs 15% in the TPC arm
- Median duration of exposure was 118 days in the HALAVEN arm and 63 days in the TPC arm[1]

EMBRACE=Eisai Metastatic Breast Cancer Study Assessing Physician's Choice versus E7389 (Eribulin); TPC=Treatment of Physician's Choice.

[a]Adverse reactions were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.[1]

[b]Based upon laboratory data.[1]

[c]Includes peripheral neuropathy, peripheral sensorimotor neuropathy, peripheral motor neuropathy (in the HALAVEN arm: all Grades=4%, Grade 3=2%), polyneuropathy, peripheral sensory neuropathy, and paresthesia.[1]

[d]Not applicable (NA); grading system does not specify greater than Grade 2 for alopecia. Rate of alopecia in the HALAVEN arm: Grade 1=26%, Grade 2=17%. Rate of alopecia in the TPC arm: Grade 1=5%, Grade 2=5%.[1,3]

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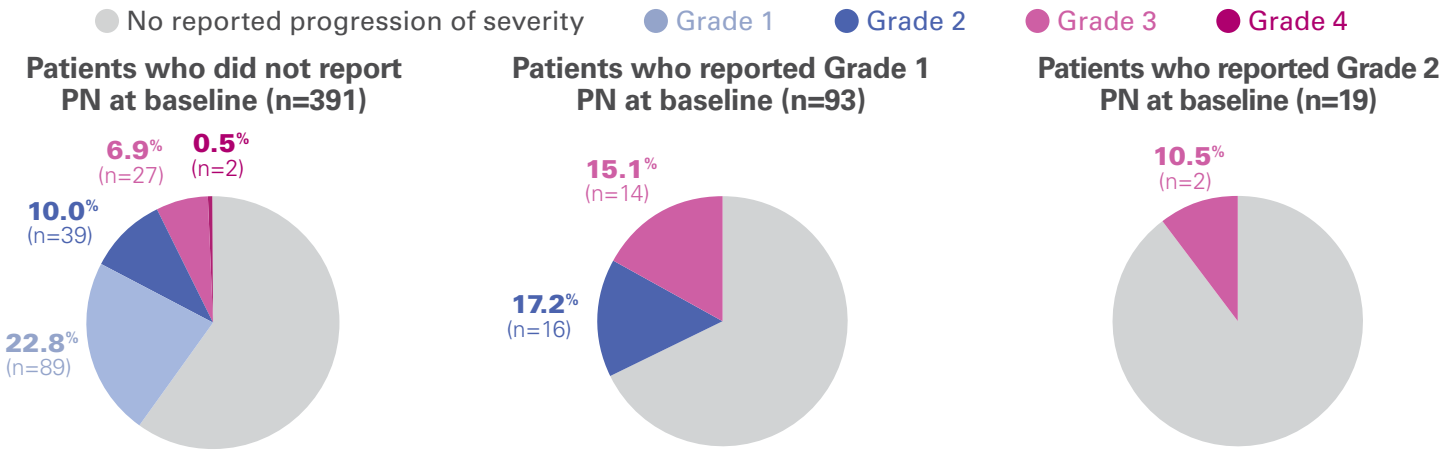
Post hoc analysis: Number of patients who reported a more severe grade of peripheral neuropathy (PN) on treatment than at baseline[4]*

WORST GRADE OF PN REPORTED DURING HALAVEN® TREATMENT[4]



*PN includes peripheral neuropathy, peripheral sensorimotor neuropathy, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, and paresthesia.

Limitation: This is a post hoc safety analysis. These are descriptive statistics and no conclusion should be drawn.

EMBRACE OVERALL SAFETY ANALYSIS

17% of enrolled patients had Grade 1 PN and 3% of patients had Grade 2 PN at baseline.[4]
PN led to discontinuation of HALAVEN in 5% of patients (24/503).[3]

EMBRACE=Eisai Metastatic Breast Cancer Study Assessing Physician's Choice versus E7389 (Eribulin).

Selected Safety Information

Warnings and Precautions (cont'd)

Peripheral Neuropathy: Grade 3 peripheral neuropathy occurred in 8% of patients with mBC (Grade 4=0.4%) and 22% developed a new or worsening neuropathy that had not recovered within a median follow-up duration of 269 days (range 25-662 days). Neuropathy lasting >1 year occurred in 5% of patients with mBC. Patients should be monitored for signs of peripheral motor and sensory neuropathy. Withhold HALAVEN in patients who experience Grade 3 or 4 peripheral neuropathy until resolution to Grade 2 or less.

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A quick 2- to 5-minute infusion

RECOMMENDED HALAVEN® ADMINISTRATION[1]

	DOSE
Recommended dose	**1.4 mg/m²**
In patients with • Mild hepatic impairment[a]	1.1 mg/m²
• Moderate hepatic impairment[b]	0.7 mg/m²
• Moderate or severe renal impairment[c]	1.1 mg/m²

[a]Mild hepatic impairment=Child-Pugh A.
[b]Moderate hepatic impairment=Child-Pugh B.
[c]Creatinine clearance (CLcr) of 15-49 mL/min.

- Patients with severe hepatic impairment (Child-Pugh C) were not studied[1]

ADMINISTER UNDILUTED OR DILUTED

- HALAVEN may be diluted in 100 mL of 0.9% Sodium Chloride Injection, USP[1]
- **Do not dilute in or administer through an intravenous line containing solutions with dextrose.** Do not administer in the same intravenous line with other medicinal products[1]
- HALAVEN is not formulated in solvents such as Cremophor® or polysorbate 80[3]

Cremophor® EL Castor Oil is a registered trademark of BASF Corporation or BASF SE.

Selected Safety Information

Warnings and Precautions (cont'd)

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

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Halaven® (eribulin mesylate) Injection | 0.5 mg/mL

A quick 2- to 5-minute infusion (cont'd)

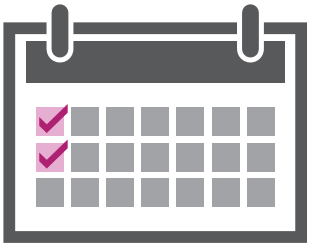
RECOMMENDED HALAVEN® ADMINISTRATION[1]

INFUSION TIME

2 to 5 minutes

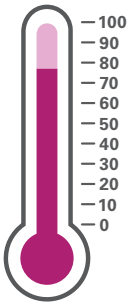
SCHEDULE

Days 1 and 8
(21-day cycle)



- **NO PREMIXING REQUIRED[1]**
- **NO KNOWN DRUG-DRUG INTERACTIONS[1]**
- **NO PREMEDICATION REQUIRED[3]**

RECOMMENDED HALAVEN STORAGE[1]



STORE AT 77°F (25°C)

- Store HALAVEN vials at 77°F (25°C); excursions permitted to 59°F-86°F (15°C-30°C)
- Do not freeze or refrigerate
- Store vials in original cartons
- Undiluted HALAVEN may be stored in the syringe for up to 4 hours at room temperature or for up to 24 hours under refrigeration (40°F or 4°C)
- Diluted HALAVEN may be stored for up to 4 hours at room temperature or for up to 24 hours under refrigeration
- Discard unused portions of the vial

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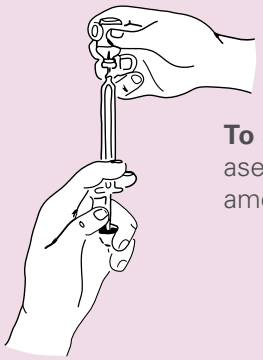
Straightforward preparation

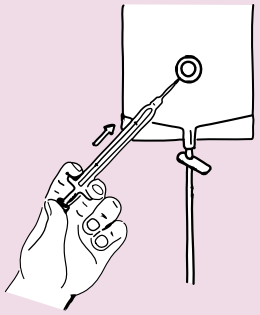
ADMINISTER UNDILUTED OR DILUTED BY IV INFUSION[1]

Each single-use vial contains 1 mg of HALAVEN® in 2 mL of solution (0.5 mg/mL)



To administer undiluted, aseptically withdraw required amount of HALAVEN from vial

OR



To dilute, aseptically withdraw required amount of HALAVEN from vial and dilute 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 with other medicinal products

Selected Safety Information

Warnings and Precautions (cont'd)

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

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Recommended dosing schedule and modifications

MANAGE ARs WITH DOSE DELAYS, REDUCTIONS, AND/OR DISCONTINUATIONS[1]*

- Assess for peripheral neuropathy and obtain complete blood cell counts prior to each dose
- Do not administer HALAVEN® on Day 1 or Day 8 in patients with ≥Grade 3 neutropenia,† ≥Grade 2 thrombocytopenia,‡ or Grade 3/4 nonhematologic toxicities
- **The Day 8 dose may be delayed for up to 1 week** in patients with toxicities
  - If toxicities resolve or improve to Grade 2 or less by Day 15, administer at a reduced dose and initiate the next cycle no sooner than 2 weeks later
  - If toxicities do not resolve or improve to Grade 2 or less by Day 15, omit the dose
- If a dose has been delayed for toxicities that have recovered to a severity of Grade 2 or less, resume at the recommended reduced dose
- If a dose has been reduced due to toxicities, do not re-escalate

EVENTS REQUIRING PERMANENT DOSE REDUCTION	CURRENT DOSE	RECOMMENDED DOSE REDUCTION
Hematologic toxicities • ANC <500/mm^3 for >7 days or ANC <1,000/mm^3 with fever or infection • Platelets <25,000/mm^3 or platelets <50,000/mm^3 requiring transfusion Grade 3/4 nonhematologic toxicities Omission or delay of Day 8 dose in previous cycle for toxicity	1.4 mg/m^2	1.1 mg/m^2
Any event requiring permanent dose reduction while receiving 1.1 mg/m^2	1.1 mg/m^2	0.7 mg/m^2
Any event requiring permanent dose reduction while receiving 0.7 mg/m^2	0.7 mg/m^2	Discontinue HALAVEN

ANC=absolute neutrophil count.
*Toxicities graded in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.[1]
†Greater than or equal to Grade 3 neutropenia=ANC <1,000/mm^3.[5]
‡Greater than or equal to Grade 2 thrombocytopenia=platelets <75,000/mm^3.[5]

Selected Safety Information

Adverse Reactions

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

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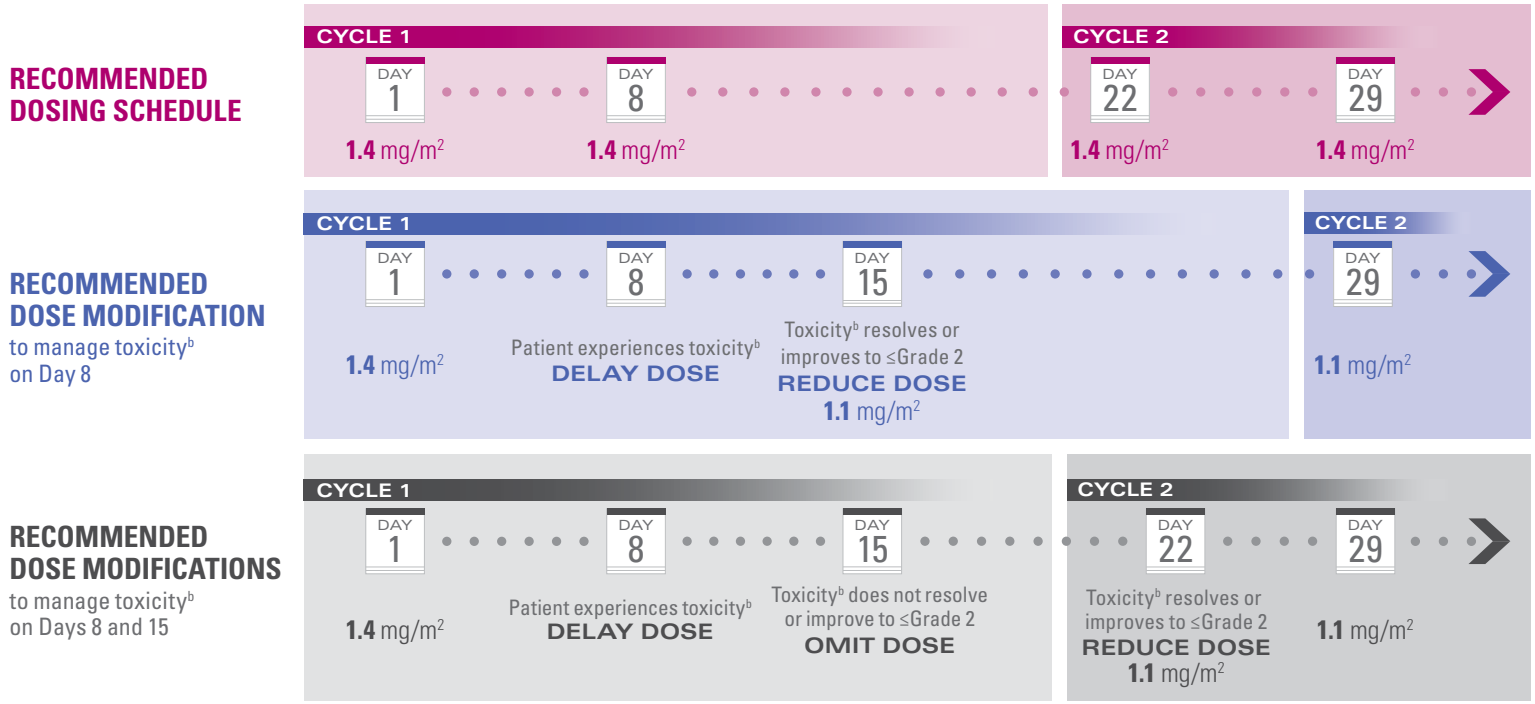
Recommended dosing schedule and modifications (cont'd)

DOSING SCHEDULE AND MODIFICATIONS[1,a]



[a]Toxicities graded in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.[1]
[b]Toxicities include ≥Grade 3 neutropenia (ANC <1,000/mm^3), ≥Grade 2 thrombocytopenia (platelets <75,000/mm^3), or Grade 3/4 nonhematologic toxicities.[1,5]

- For any event requiring permanent dose reduction while receiving 1.1 mg/m^2, reduce to 0.7 mg/m^2 of HALAVEN®[1]
- For any event requiring permanent dose reduction while receiving 0.7 mg/m^2, discontinue HALAVEN[1]

Selected Safety Information

Use in Specific Populations

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

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HALAVEN® SAFETY AND DOSING INFORMATION

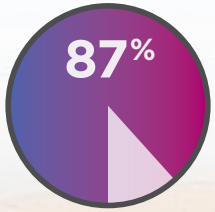
HALAVEN FOR PATIENTS WITH THIRD-LINE mBC[1]

HALAVEN may be appropriate for your patients, regardless of their subtype, who are ready for chemotherapy in third-line mBC and who have received 2 prior chemotherapies for mBC. Their previous treatment should have included an anthracycline and a taxane in the adjuvant or metastatic setting.

A Growing Body of Real-world Experience

in more than 70 countries, with over 65,000 patients in the US[3†]

87% of Patients **DID NOT** Have Adverse Events Leading to Discontinuation



13% of patients receiving HALAVEN had adverse events leading to discontinuation vs 15% in the TPC arm[2]

Quick 2- to 5-Minute Infusion Time

mBC=metastatic breast cancer; TPC=Treatment of Physician's Choice.
*Indications may differ in other countries.
†Patient treatment based on estimate of average patient usage provided by IntrinsiQ® intelliVIEW™. Total number of vials from November 2010 to March 2020.

References: 1. HALAVEN [package insert]. Woodcliff Lake, NJ: Eisai Inc. **2.** Cortes J, O'Shaughnessy J, Loesch D, et al; EMBRACE (Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389) investigators. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomized study. *Lancet.* 2011;377(9769):914-923. **3.** Data on file, Eisai Inc. **4.** Kaufman PA, Olivo M, He Y, McCutcheon S, Vahdat L. Peripheral neuropathy in patients with metastatic breast cancer treated with eribulin: resolution and association with efficacy. Poster presented at: American Society of Clinical Oncology Annual Breast Cancer Symposium; September 4-6, 2014; San Francisco, CA. **5.** National Cancer Institute. Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events v3.0. NIH publication 03-5410. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf. Published March 31, 2003. Updated August 9, 2006. Accessed March 11, 2020.

Selected Safety Information

Use in Specific Populations (cont'd)

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

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Price disclosure information for prescribers available at us.eisai.com/RequiredPriceDisclosures.

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