Drug Monograph

A - Drug Name

eriBULin

COMMON TRADE NAME(S): Halaven® (Eisai)

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B - Mechanism of Action and Pharmacokinetics

eriBULin is a synthetic form of halichondrin B, an agent isolated from the sea sponge *Halichondria okadai*. It is a non-taxane microtubule dynamic inhibitor which suppresses the polymerization of microtubules and sequesters tubulin into nonproductive aggregates. Its action is distinct from the vinca alkaloids, taxanes and epothilones that affect both microtubule growth or shortening. The antimitotic action of eriBULin leads to cell apoptosis due to G2/M cell cycle-block.

Absorption	Pharmacokinetics is dose-proportional and linear. No significant eriBULin accumulation is observed on weekly administration. Gender and race do not have significant effects on eriBULin pharmacokinetics.	
Distribution	Rapid distribution phase	
	PPB	49-65%
Metabolism	Negligible metabolism by CYP3A4. eriBULin is also a substrate of P-gp, but the contribution of this transporter to the biliary and renal elimination of eriBULin is unknown. No major human metabolites are found.	
	Inactive metabolites	Trace (0.6% concentration of parent compound)

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Elimination	Triphasic drug concentration decline with a long elimination phase. eriBULin is mainly eliminated unchanged.	
	Feces	82%
	Urine	9%
	Half-life	40 hours

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C - Indications and Status

Health Canada Approvals:

For the treatment of patients with metastatic breast cancer who have previously received at least 2 chemotherapeutic regimens for treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane administered in either the adjuvant or metastatic setting.

For the treatment of paitents with unresectable or metastatic liposarcoma, a subtype of soft tissue sarcoma. Prior therapy should have included an anthracycline-containing regimen, if clinically appropriate.

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D - Adverse Effects

Emetogenic Potential: Low

Extravasation Potential: Minimal

The following adverse effects were reported in the pivotal trial in metastatic breast cancer patients (EMBRACE) or were severe or life-threatening.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Atrial fibrillation (rare)	E
	Hypertension (<10%)	E
	QT interval prolonged (<10%)	E
	Venous thromboembolism (rare)	E

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Dermatological	Alopecia (45%)	D
	Hand-foot syndrome (1%)	E
	Rash (<10%; may be severe)	E
Gastrointestinal	Abdominal pain (<10%)	E
	Anorexia, weight loss (21%)	E
	Constipation (25%)	E
	Diarrhea (18%)	E
	Mucositis (9%)	E
	Nausea, vomiting (35%)	I
General	Edema (<10%)	E
	Fatigue (54%)	E
Hematological	Disseminated intravascular coagulation (rare)	E D
	Myelosuppression ± infection, bleeding (58%) (severe)	E
Hepatobiliary	↑ LFTs (73%) (may be severe)	E
	Pancreatitis (rare)	E
Hypersensitivity	Hypersensitivity (rare)	I
Metabolic / Endocrine	Abnormal electrolyte(s) (38%)	E
	Hyperglycemia (<10%)	E
Musculoskeletal	Musculoskeletal pain (22%)	E
Nervous System	Anxiety /depression/ insomnia (<10%)	E
	Dizziness (<10%)	E
	Dysgeusia (<10%)	E
	Headache (19%)	E
	Neuropathy (35%) (8% severe)	E D
	Other - Pharyngolaryngeal pain (<10%)	E
	Vertigo (<10%)	E
Ophthalmic	Conjunctivitis (<10%)	E
Renal	Creatinine increased (14%)	E
Respiratory	Cough, dyspnea (16%)	E
	Pneumonitis (rare)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.
Dose-limiting side effects are underlined.

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** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for eriBULin include ↑ lfts, myelosuppression ± infection, bleeding, fatigue, alopecia, abnormal electrolyte(s), nausea, vomiting, neuropathy, constipation, pain, anorexia and weight loss.

Myelosuppression usually manifests as neutropenia, is dose dependent and may be severe in some cases. Patients with elevated LFTs (> 3 x ULN; bilirubin > 1.5 x ULN) had higher incidences of grade 4 neutropenia and febrile neutropenia than patients with normal liver function tests.

Neuropathy was the most common toxicity leading to treatment discontinuation in the pivotal trial. It is dose-limiting and 5% of patients experienced neuropathy that lasted more than one year.

QT prolongation appeared to be a delayed effect as it has been observed on day 8 (maximum 11.4 msec from baseline) in a non-controlled trial, but this was not observed on day 1.

Severe rashes, including SJS and TENS have been reported.

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E - Dosing

Refer to protocol by which patient is being treated. Do not start the first dose until platelets are > 100 x 10^9/L and ANC ≥ 1.5 x 10^9/L. Correct electrolyte abnormalities prior to treatment, especially potassium, calcium and magnesium. Do not re-escalate a dose reduced for toxicity.

Adults:

Intravenous: 1.4 mg/m² (as eriBULin mesylate) on day 1 and day 8 every 3 weeks

Starting Dose	Dose level -1	Dose level -2	Dose level -3
1.4 mg/m^2	1.1 mg/m^2	0.7 mg/m^2	Discontinue

Dosage with Toxicity:

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Dose adjustments on Day 1 or Day 8:

Worst toxicity in previous period / on day of dosing	**Day 1***	**Day 8 */#**
Platelets < 75-100 x 10^9/L or ANC <1-1.5 x 10^9/L on day of dosing	Do not treat *	Delay for one week; if no recovery, omit for that cycle
Grade 4 ANC > 7 days, Grade 4 thrombocytopenia, Febrile neutropenia, Platelets < 50 requiring transfusion or Thrombocytopenic bleeding	Hold until recovered*, then ↓ 1 dose level	Delay for one week; if no recovery, omit for that cycle
≥ grade 3 non-hematologic	Hold until recovered*, then ↓ 1 dose level	Delay for one week until ≤ grade 2; if no recovery, omit for that cycle
Delay or dose modification for day 8 in previous cycle	↓ one dose level for all subsequent doses	

* Do not treat until ANC ≥ 1 x 10^9/L and platelets ≥ 75 x 10^9/L and other toxicity ≤ grade 2.
# If delay day 8, the cycle length is also increased (next cycle must be ≥2 weeks after the delayed "day 8").

Dosage with Hepatic Impairment:

eriBULin exposure is increased in mild and moderate hepatic impairment. Starting doses should be reduced and patients monitored closely for toxicity.

Hepatic function	**Recommended Dose on Days 1 and 8 (mg/m^2)**
Normal (bilirubin < 1.5 x ULN, transaminases ≤ 3 x ULN)	1.4
Mild impairment (Child Pugh A)	1.1
Moderate impairment (Child Pugh B)	0.7
Severe impairment (Child Pugh C)	OMIT

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Dosage with Renal Impairment:

Mild or moderate renal impairment may decrease eriBULin clearance. Exposure may increase up to 1.5-fold in moderate or severe renal impairment. Monitor for adverse effects, especially myelosuppression.

Renal impairment	Starting dose
Mild (50-80 mL/min)	No change in starting dose
Moderate or severe (15-50 mL/min)	Caution; ↓ starting dose to 1.1 mg/m2
End-stage (<15 mL/min)	No data; OMIT

Dosage in the elderly:

No dose adjustments required.

Children:

Safety and effectiveness in pediatric patients have not been established.

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F - Administration Guidelines

- Give IV over 2 to 5 minutes
- Dose may be administered in a syringe without dilution or may dilute in up to 100mL NS.
- Does not require premedications with steroids and/or antihistamines for hypersensitivity.
- Do not admix eriBULin with other medicinal products.
- Do not dilute or administer with dextrose-containing solutions.
- Store unopened vials at room temperature in their original cartons.
- Diluted solutions may be stored for up to 48 hours refrigerated, or for up to 24 hours at room temperature.

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug, halichondrin B or any of its components
- Severe hepatic impairment
- End-stage renal disease

Other Warnings/Precautions:

- Avoid use in patients with congenital long QT syndrome.
- Avoid concomitant use of QT-prolonging drugs, where possible (see Drug Interactions).
- Correct any hypocalcemia, hypokalemia and hypomagnesemia prior to starting eriBULin.
- Exercise extreme caution with significant cardiovascular impairment (congestive heart failure > grade 2, unstable angina or myocardial infarction within the last 6 months) as the safety of eriBULin in this population has not been established.
- Use with caution in patients with pre-existing neuropathy as eriBULin may aggravate the condition.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Genotoxicity: Documented in animals
- Mutagenicity: No
- Embryotoxicity: Documented in animals
- Fetotoxicity: Documented in animals
- Teratogenicity: Documented in animals
  eriBULin is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least 3 months after the last dose.
- Breastfeeding: Not recommended
- Fertility effects: Probable
  May be irreversible. Male patients should seek advice on conservation of sperm prior to treatment.

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H - Interactions

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eriBULin is not expected to alter the plasma concentrations of drugs that are substrates of CYP1A2, 2C9, 2C19, 2D6, 2E1 or 3A4. No drug-drug interactions are expected with CYP3A4 inhibitors or inducers.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Inhibitors of transport proteins, such as P-gp (i.e. quinidine, verapamil, cyclosporine)	↑ eriBULin exposure (theoretical)	↓ drug efflux	Caution and monitor for toxicity
Drugs that may prolong QT (i.e. amiodarone, procainamide, sotalol, venlafaxine, amitriptyline, sunitinib, methadone, chloroquine, clarithromycin, haloperidol, fluconazole, moxifloxacin, domperidone, ondansetron, etc)	↑ risk of QT prolongation	Additive	Avoid where possible. Monitor with ECG if used together.
Drugs that disrupt electrolyte levels (i.e. loop/thiazide diuretics, laxatives, amphotericin B, high dose corticosteroids)	↑ risk of QT prolongation	electrolyte imbalance	Caution; monitor ECG

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

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Monitor Type	Monitor Frequency
CBC	Baseline and before each dose; more frequent in patients who develop severe myelosuppression.
Liver and renal function tests, including electrolytes	Baseline and before each dose
ECG in patients with risk factors for torsade de pointes (i.e. patients with cardiac disease or concomitant QT-prolonging medications)	Baseline and as clinically indicated
Clinical toxicity assessment for neuropathy, cardiotoxicity, hepatic, musculoskeletal, fatigue, GI symptoms and thromboembolism	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Supplementary Public Funding

New Drug Funding Program (

NDFP Website

)

- Eribulin - Metastatic or Incurable Locally Advanced - Breast Cancer

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K - References

Eribulin: AHFS Drug Information. October 2011. Available from: http://www.ahfsdruginformation.com

Eribulin mesylate. NCI Drug Dictionary - National Cancer Institute. Available from: http://www.cancer.gov/drugdictionary?cdrid=257773

NCCN Clinical Practice Guidelines in Oncology: Antiemesis: Version 1, 2012.

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Perry CM. Eribulin. Drugs 2011;71(10):1321-31.

Product Monograph: Halaven® (eribulin). Eisai Limited, August 2017.

Product Monograph: Halaven® (eribulin). Eisai Inc. (US), November 2010.

January 2018 added new indication for liposarcoma; updated adverse effects

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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