DRUG NAME: Eribulin

SYNONYM(S): Eribulin mesylate

COMMON TRADE NAME(S): HALAVEN®

CLASSIFICATION: antimicrotubule agent

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Eribulin is a non-taxane microtubule dynamics inhibitor, belonging to a new class of antineoplastic agents, the halichondrin class. Eribulin inhibits the formation of mitotic spindles and blocks cell cycle progression at the G_2/M phase, resulting in apoptotic cell death. However, unlike other antimicrotubule agents (e.g. taxanes, vinca alkaloids), eribulin inhibits the growth phase without affecting the microtubule shortening phase and also sequesters tubulin into nonfunctional aggregates, thereby exhibiting activity against taxane-resistant cells.[1]

PHARMACOKINETICS:

Distribution	rapid	
	cross blood brain barrier?	no information found
	volume of distribution	43-114 L/m^2
	plasma protein binding	49-65%
Metabolism	negligible	
	active metabolite(s)	none
	inactive metabolite(s)	none
Excretion	predominantly as unchanged drug	
	urine[2]	9%
	feces[2]	82%
	terminal half life	40 h
	clearance	1.16-2.42 L/h/m^2

Adapted from standard reference[1] unless specified otherwise.

USES:

Primary uses:
*Breast cancer

*Health Canada approved indication

Other uses:

SPECIAL PRECAUTIONS:

Contraindications:
- history of hypersensitivity reaction to eribulin or halichondrin B or its chemical derivatives[1]
- congenital long QT/QTc syndrome[1]

Caution:

- ***QT/QTc interval prolongation*** has been observed with eribulin. Baseline and periodic ECG and electrolyte monitoring are suggested in patients at risk for developing torsades de pointes, including those with cardiac disease, history of arrhythmias, electrolyte disturbances, nutritional deficits, and other risk factors for QT interval prolongation. Concurrent therapy with other QT/QTc-prolonging drugs may increase the risk of potentially fatal arrhythmias and should be avoided if possible.[1]
- Correct ***electrolyte disturbances*** prior to treatment; use caution with drugs that may disrupt electrolyte levels.[1]
- ***Peripheral neuropathy*** has been observed with eribulin; use with caution in patients with pre-existing neuropathy.[1]
- Consider dose reduction in ***mild to moderate hepatic***[1] or ***moderate renal impairment***[2]; see **Dosage Guidelines**.

Carcinogenicity: no information found.

Mutagenicity: Not mutagenic in Ames test. Eribulin is mutagenic in a mammalian *in vitro* mutation test and clastogenic in a mammalian *in vivo* chromosome tests.[1]

Fertility: Testicular toxicity has been reported in animals, including soft and/or small testes, decreased testicular weight, hypocellularity or degeneration of seminiferous tubules. Testicular changes were associated with secondary epididymal hypospermia/aspermia. In rats, there is indication that testicular damage may be irreversible. Men are advised to conserve sperm prior to treatment with eribulin if planning to father children in the future.[1]

Pregnancy: FDA Pregnancy Category D.[3] There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
Embryo-fetal toxicity and teratogenicity have been reported in animal studies, at doses less than human recommended doses. Decreased fetal weight, external and/or soft tissue anomalies (absence of lower jaw, tongue, stomach and spleen) and early delivery have been reported.[1] As a microtubule inhibitor, eribulin is expected to cause fetal harm when administered to pregnant women. Contraception is recommended during treatment and for at least 3 months after treatment.[4]

Breastfeeding is not recommended due to the potential secretion into breast milk.

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[5]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (58-78%, severe <1-2%)[1,2]
	febrile neutropenia (5%)
	neutropenia (82%, severe 29%); nadir 13 days, recovery 8 days
	thrombocytopenia (20%, severe 1%)
cardiac	***QT-interval prolongation***
	tachycardia (3-10%)
ear and labyrinth	vertigo (3-10%)
gastrointestinal	*emetogenic potential: low*[6]
	abdominal pain (1-10%)[1,2]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	stomatitis, mucosal inflammation (5-18%)[1,2]
	constipation (25%, severe <1%)
	diarrhea (18%)
	nausea (35%, severe <1%)
	pancreatitis (<1%)
	vomiting (18%, severe 1%)
general disorders and administration site conditions	*extravasation hazard: none*
	asthenia/fatigue (54%, severe 1-9%)
	peripheral edema (1-10%)[1,2]
	pyrexia (21%, severe <1%)
	urinary tract infection, upper respiratory tract infection (1-10%)[1,2]
investigations	ALT increase (3-18%)[1,2]
	AST increase (3-10%)
	bilirubin abnormality (3%, severe 1%)
	creatinine abnormality (3%, severe 1%)
	weight loss (21%, severe 1%)
metabolism and nutrition	anorexia (20%, severe 1%)
	hypercalcemia/hypocalcemia (4-7%, severe 1-2%)
	hyperkalemia/hypokalemia (3-10%, severe 1-4%)
	hypermagnesemia/hypomagnesemia (3-10%, severe 1-4%))
musculoskeletal and connective tissue	arthralgia/myalgia (22%, severe <1%)
	back and limb pain (11-16%)
	bone pain (12%, severe 2%)
nervous system	dizziness (1-10%)[1,2]
	headache (10-19%, severe <1%)[1,2]
	peripheral neuropathy (35%, severe 8%)
psychiatric	anxiety (3-10%)
	depression, insomnia (1-10%)[1,2]
respiratory, thoracic and mediastinal	cough (14%)
	dyspnea (16%, severe 1-4%)
skin and subcutaneous tissue	alopecia (45%)
	pruritus (3-10%)
	rash (1-10%)[1,2]
vascular	hypertension (3-10%)

Adapted from standard reference[1] unless specified otherwise.

INTERACTIONS:

Avoid concurrent use of QT/QTc-prolonging drugs if possible. ECG monitoring is recommended. Use caution with drugs that may disrupt electrolyte levels.[1]

SUPPLY AND STORAGE:

***Injection*:** Eisai Limited supplies eribulin injection as 1 mg single use, ready-to-use vials in a concentration of 0.5mg/mL. Vials contains 5% (v/v) dehydrated alcohol. Store at room temperature. Do NOT freeze. Protect from light.[1]

For basic information on the current brand used at the BC Cancer Agency, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at the BC Cancer Agency, see Chemotherapy Preparation and Stability Chart in Appendix.

Additional information:
- Do not dilute with or administer through an intravenous line containing dextrose solutions.[1]
- May be administered undiluted or diluted in up to 100 mL NS.[4]

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BCCA administration guideline noted in ***bold***, ***italics***

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	***administer over 2 to 5 minutes[1,7]***
Intermittent infusion	administer over 2 to 5 minutes[1]; may be infused up to 60 minutes[3]
Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	no information found

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

BCCA usual dose noted in ***bold, italics***

Intravenous[4,7]:	Cycle Length: 3 weeks:	***1.4 mg/m²*** (range 0.7-1.4 mg/m²) ***IV for one dose on days 1 and 8*** (total dose per cycle 2.8 mg/m² [range 1.4-2.8 mg/m²])
Concurrent radiation:	no information found	

BCCA usual dose noted in ***bold, italics***

Dosage in myelosuppression[1]*:*

Cycle Length:
modify according to protocol by which patient is being treated; if no guidelines available, the following have been suggested:

- do not administer on day 1 or day 8 if ANC <1 x 10^9 OR Platelets <75 x 10^9 OR any grade 3/4 non-hematological toxicities.
- day 8 dose may be delayed for a maximum of 1 week; omit dose if toxicities do not improve to ≤grade 2 by day 15.
- may resume treatment on day 15 at a reduced dose if toxicities improve to ≤grade 2 (except anemia). See table below for recommended dose adjustments. Wait at least 2 weeks before starting next treatment cycle.
- do not re-escalate dose after dose reduction.

Dose Modification for Toxicity	
Permanently reduce from 1.4 mg/m^2 for any of the following toxicities: • ANC <0.5 x 10^9 for >7 days • ANC <1 x 10^9 with fever or infection • platelets < 25 x 10^9 • platelets <50 x 10^9 requiring transfusion • non-hematologic grade 3 or 4 toxicities • omission or delay of day 8 dose in previous cycle for toxicity	New Dose 1.1 mg/m^2
If any of the above events occurs while receiving 1.1mg/m^2	0.7 mg/m^2
If any of the above events occurs while receiving 0.7 mg/m^2	discontinue treatment

Dosage in renal failure[4]:

modify according to protocol by which patient is being treated; if no guidelines available, the following have been suggested:

Creatinine clearance (mL/min)	**Dose** (IV on days 1 and 8)
>50	1.4 mg/m^2
15-50	1.1 mg/m^2
<15	no information found

Calculated creatinine clearance = $\frac{N^* \times (140 - Age) \times \text{weight in kg}}{\text{Serum Creatinine in µmol/L}}$

* For males N=1.23; for females N=1.04

Dosage in hepatic failure[1]*:*

Degree of hepatic impairment	**Dose** (IV on days 1 and 8)
Mild (Child-Pugh class A)	1.1 mg/m^2
Moderate (Child-Pugh class B)	0.7 mg/m^2
Severe (Child-Pugh class C)	no information found

Dosage in dialysis:

no information found

Children:

no information found

REFERENCES:

1. Eisai Limited. HALAVEN® product monograph. Mississauga, Ontario; 17 January 2013.
2. Lexi-Drugs® (database on the Internet). Eribulin. Lexi-Comp Inc., 17 April 2013. Available at: http://online.lexi.com. Accessed 23 July 2013.
3. AHFS Drug Information® (database on the Internet). Eribulin mesylate. Lexi-Comp Inc., 2 April 2013. Available at: http://online.lexi.com. Accessed 23 July 2013.
4. Eisai Limited. HALAVEN® product monograph. Mississauga, Ontario; 21 January 2015.
5. Vanessa Bernstein MD. Personal communication. BC Cancer Agency Breast Tumour Group; 4 December 2013.
6. BC Cancer Agency. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer Agency; 1 Mar 2012.
7. BC Cancer Agency Breast Tumour Group. (UBRAVERIB) BCCA Protocol Summary for Palliative Therapy for Metastatic Breast Cancer using Eribulin. Vancouver, British Columbia: BC Cancer Agency; 1January 2014.