eriBULin Monotherapy – 28 Day[i]

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Treatment of locally advanced or metastatic breast cancer which has progressed after at least one chemotherapeutic regimen for advanced disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting unless patients were not suitable for these treatments.	C50	00743a	ODMS

* This is for post 2012 indications only.

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

eriBULin is administered on day 1 and 15 of a 28 day cycle until disease progression or unacceptable toxicity occurs.

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1 and 15	[a, b, c]eriBULin	1.23mg/m^2	IV infusion	[d, e] 50ml 0.9% NaCl over 5 minutes	Every 28 days
[a]Note: eriBULIn may be used in combination with trastuzumab therapy (Ref NCCP Regimen 00200 Trastuzumab (IV) Monotherapy - 21 days).					
[b]In the EU the recommended dose refers to the base of the active substance (eriBULin). Calculation of the individual dose to be administered to a patient must be based on the strength of the ready to use solution that contains 0.44 mg/ml eriBULin and the dose recommendation of 1.23 mg/m^2. The dose reduction recommendations shown below (Table 1, 2 and 3) are also shown as the dose of eriBULin to be administered based on the strength of the ready to use solution.					
[c]In the pivotal EMBRACE trial, the corresponding publication and in some other regions e.g. the US and Switzerland, the recommended dose is based on the salt form (eriBULin mesylate). The equivalent dose of eriBULin mesylate is 1.4mg/m^2.					
[d]eriBULin should not be diluted in 5% glucose.					
[e] Final dose concentration should be 0.018 - 0.18mg/ml.					

ELIGIBILITY:

- Indications as above
- ECOG 0-2
- Platelets > 100 x 10^9/L and ANC ≥ 1.5x10^9/L

EXCLUSIONS:

- Hypersensitivity to eriBULin or to any of the excipients
- Breast feeding
- Congenital long QT syndrome

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profile
- ECG monitoring if therapy initiated in patients with congestive heart failure, bradyarrhythmias, medicinal products known to prolong the QT interval, including Class Ia and III antiarrhythmics, and electrolyte abnormalities.

Regular tests:

- FBC, renal and liver profile at the start of each cycle.
- ECG monitoring if clinically indicated as above.

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.
- The administration of eriBULin should be delayed on day 1 or day 15 for any of the following:
  - ANC < 1 x 10^9/L
  - Platelets < 75 x 10^9/L
  - Grade 3 or 4 non-haematological toxicities

Thereafter the dose modifications in Table 1 apply.

Haematological:

Table 1: Dose modification of eriBULin in haematological toxicity

ANC (x10^9/L)	**Dose**
< 0.5 lasting > 7 days	0.97mg/m^2
< 1.0 complicated by fever or infection	
Platelets(x10^9/L)	
< 25	
< 50 complicated by haemorrhage or requiring blood or platelet transfusion	
Reoccurrence of any haematological adverse reactions as specified above	
Despite reduction to 0.97mg/m^2	0.62mg/m^2
Despite reduction to 0.62mg/m^2	Consider discontinuation
Do not re-escalate the eriBULin dose after it has been reduced.	

Renal and Hepatic Impairment:

Table 2: Dose modification of eriBULin in renal and hepatic impairment

Renal Impairment		**Hepatic Impairment**	
CrCl (ml/min)	**Dose**	**Grade**	**Dose**
<50	80% of original dose	Mild (Child-Pugh A)	80% of the original dose
		Moderate (Child-Pugh B)	50% of the original dose
Haemodialysis	80% of original dose may be considered	Severe (Child-Pugh C)	Not recommended

Management of adverse events:

Table 3: Dose Modification of eriBULin for Adverse Events

Adverse reactions	**Recommended dose modification**
Grade 3 or 4 non haematological toxicity in previous cycle.	Reduce dose from 1.23mg/m^2 to 0.97mg/m^2. If there is any reoccurrence despite the dose reduction, reduce dose further to 0.62mg/m^2. If there is any reoccurrence despite dose reduction to 0.62mg/m^2, consider discontinuation. Do not re-escalate the eriBULin dose after it has been reduced.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Low **(Refer to local policy).**

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE:

- Severe neutropenia may be managed by the use of G-CSF.
- eriBULin may cause adverse reactions such as tiredness and dizziness which may lead to a minor or moderate influence on the ability to drive or use machines. Patients should be advised not to drive or use machines if they feel tired or dizzy.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Haematology:** Myelosuppression is dose dependent and manifests primarily as neutropenia. Patients experiencing febrile neutropenia, severe neutropenia or thrombocytopenia should be treated according to the recommendations in Table 1 above. Patients with ALT or AST > 3 x ULN experienced a higher incidence of Grade 4 neutropenia and febrile neutropenia. Although data are limited, patients with bilirubin > 1.5 x ULN also have a higher incidence of Grade 4 neutropenia and febrile neutropenia.
- **Peripheral neuropathy:** Patients should be closely monitored for signs of peripheral motor and sensory neuropathy. The development of severe peripheral neurotoxicity requires a delay or reduction of dose.
- **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, bradyarrhythmias, medicinal products known to prolong the QT interval, including Class Ia and III anti-arrhythmics, and electrolyte abnormalities. Hypokalemia, hypocalcaemia or hypomagnesaemia should be corrected prior to initiating eriBULin and these electrolytes should be monitored periodically during therapy.

DRUG INTERACTIONS:

- No drug-drug interactions are expected with CYP3A4 inhibitors and inducers
    - However, caution and monitoring for adverse events is recommended with concomitant use of substances that have a narrow therapeutic window and that are eliminated mainly via CYP3A4-mediated metabolism (e.g. alfentanil, cyclosporine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus)
- Increased risk of QT prolongation with drugs that disrupt electrolyte levels and Class Ia and III anti-arrhythmics.

- Ondansetron may prolong QT interval, consider alternative antiemetic in combination with eriBULin for patients predisposed to QT prolongation
- Current drug interaction databases should be consulted for more information.

REFERENCES:

1. Ohtani S, et al. Bi-weekly eribulin therapy for metastatic breast cancer: a multicentre phase II prospective study (JUST STUDY). Breast Cancer (2018) 25:438–446.
2. Smith J, et al. Phase II Study of Eribulin Mesylate Administered Biweekly in Patients with Human Epidermal Growth Factor Receptor-2 Negative Metastatic Breast Cancer. Clinical Breast Cancer (2019) 20:160-167
3. Cortes J, O'Shaughnessy J, Loesch D et al. EriBULin monotherapy versus treatment of physicians choice in patients with metastatic breast cancer (EMBRACE): a phase three open label randomized study. Lancet 2011; 377 (9769): 914-923.
4. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://pubmed.ncbi.nlm.nih.gov/37269847/
5. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
6. eriBULin (HALAVEN®) Summary of Product Characteristics. Accessed March 2024. Available at https://www.ema.europa.eu/en/documents/product-information/halaven-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	11/07/2022		Prof Cathy Kelly
2	02/12/2022	Amended infusion volume	Prof Maccon Keane
3	11/04/2024	Reviewed. Updated renal and hepatic dose modifications, drug interactions section.	Prof Cathy Kelly

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] 'This is an unlicensed posology for the use of eriBULin in Ireland. Patients should be informed of this and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be fully aware of their responsibility in communicating any relevant information to the patient and also ensuring that the unlicensed or "off label" indication has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.'