Bortezomib, dexAMETHasone, Thalidomide, CISplatin, DOXOrubicin, cycloPHOSphamide and Etoposide (VDT PACE) Therapy[i]

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Failure to achieve response or disease progression with induction therapy in patients with multiple myeloma	C90	00496a	N/A
Relapsed or refractory myeloma patients suitable for intensive salvage chemotherapy.	C90	00496b	N/A
Treatment of multiple myeloma in patients with primary plasma cell leukaemia or initial presentation with extra-medullary disease	C90	00496c	N/A

* 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.

Treatment is administered as per the table below every 28 days (once counts have recovered) for a maximum of 6 cycles.

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

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1-4	dexAMETHasone	40mg	PO	N/A	Every 28 days
1-28	Thalidomide	100mg[a] (preferably nocte)	PO	N/A	Every 28 days
1-4	CISplatin[b]	10mg/m^2	IV infusion	500 mL NaCl 0.9% over 24 hours	Every 28 days
1-4	Etoposide	40mg/m^2	IV infusion	500 mL NaCl 0.9% over 24 hours	Every 28 days
1-4	cycloPHOSphamide	400mg/m^2	IV infusion	250 mL NaCl 0.9% over 24 hours	Every 28 days
1-4	DOXOrubicin[d]	10mg/m^2	IV infusion	250ml NaCl 0.9% over 24 hours	Every 28 days
1, 4, 8 and 11	Bortezomib[e]	1.0 mg/m^2	S/C [f] (abdomen or thigh)[g]	N/A	Every 28 days
6 onwards (Filgrastim to start 24 hours after the completion of chemotherapy)	G-CSF	5mcg/kg	SC	N/A	Daily until ANC > 1 x 10^9/L

[a] Patients may be started at a dose of thalidomide 50mg at the discretion of the prescribing consultant.

[b] **Pre-Hydration therapy required for CISplatin** See local hospital policy recommendations. **Suggested prehydration for CISplatin:** • 1000mL 0.9% NaCl with 20 mmol KCl (potassium chloride) and 8 mmol magnesium sulphate 12 hourly via continuous IV infusion on Day 1 – Day 4. **(Refer to relevant local hospital policy for advice on administration of electrolyte infusions).** • Administer CISplatin as described above
[c]cycloPHOSphamide may also be administered as an IV bolus over 5-10mins.
[d] Lifetime cumulative dose of DOXOrubicin is 450mg/m^2. **In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors outlined below [ii] and to the age of the patient.**
[e] Bortezomib is a proteasome inhibitor and is neurotoxic. Refer to *NCCP Guidance on the Safe Use of Neurotoxic drugs (including Vinca Alkaloids) in the treatment of cancer here*.
[f] Note: In individual cases where approved by Consultant bortezomib may be administered as IV bolus over 3-5 seconds through a peripheral or central intravenous catheter followed by a flush with 0.9% NaCl. Note the concentration of bortezomib solution should be 1mg/ml when administered via the IV route.
[g] The solution should be injected subcutaneously, at a 45-90^0 angle. Injection sites should be rotated for successive injections. If local injection site reactions occur, either a less concentrated solution may be administered s/c or a switch to intravenous injection is recommended. At least 72 hours should elapse between consecutive doses of bortezomib.

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

ELIGIBILITY:

- Indications as above
- Patients with pre-existing severe neuropathy should be treated with bortezomib and thalidomide only after careful risk/benefit assessment. Caution should be exercised as further treatment may result in severe prolonged neuropathy.
- Adequate haematologic, renal and hepatic function

CAUTIONS:

- Congestive heart failure (LVEF < 50%) or other significant heart disease.

EXCLUSIONS:

- Hypersensitivity to thalidomide, CISplatin, etoposide, cycloPHOSphamide, DOXOrubicin, bortezomib, boron, dexAMETHasone or any of the excipients
- Patients who are unable to comply with the Thalidomide Pregnancy Prevention Programme
- Severe renal impairment
- Significant hearing impairment/tinnitus
- Pregnancy
- Breast Feeding
- Acute diffuse infiltrative pulmonary and pericardial disease

PRESCRIPTIVE AUTHORITY:

- The treatment plan must be initiated by a Consultant Haematologist working in the area of haematological malignancies

TESTS:

Baseline tests:

- FBC, renal, liver and bone profile
- Uric acid
- Clotting screen
- Blood pressure, *blood glucose if being treated with oral hypoglycaemics. (* See Drug Interactions)
- Assessment of peripheral neuropathy status
- Urine pregnancy testing or serum hCG test for women of childbearing potential as per Pregnancy Prevention Programme
- Assessment and registration as per Pregnancy Prevention Programme for both male and female patients.
- Audiology and creatinine clearance if clinically indicated
- ECG
- MUGA or ECHO (LVEF > 50% to administer DOXOrubicin) if >65 years or if clinically indicated
- Virology screen - Hepatitis B (HBsAg, HBcoreAb), hepatitis C, HIV
  ***(Reference Adverse Events/Regimen Specific Complications for information on Hepatitis B reactivation)**

Regular tests:

- FBC; monitor platelet count **at a minimum** of day 1 and day 11 each cycle
- Renal, liver and bone profile prior to each cycle.
- Blood pressure, *blood glucose if being treated with oral hypoglycaemics. (* See Drug Interactions)
- Urine pregnancy testing or serum hCG test every 28 days for women of childbearing potential as per Pregnancy Prevention Programme
- If clinically indicated creatinine, MUGA scan or echocardiogram

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.

Haematological:

- Where cytopenias are considered to be SACT induced, delay subsequent cycles until ANC ≥1.0 x 10^9/L and platelets ≥75 x10^9/L
- Where cytopenias are secondary to bone marrow infiltration, dose modification may not be indicated – clinical decision

Renal and Hepatic Impairment:

Table 1: Dose modification in renal and hepatic impairment

Drug	Renal Impairment		Grade of Hepatic Impairment*	Bilirubin Level	SGOT (AST) levels	Modification of starting dose
Bortezomib	Renal impairment: no dose adjustment is needed Haemodialysis: no dose adjustment is needed, administer after haemodialysis		Mild	≤1 x ULN	> ULN	None
				>1 - 1.5 x ULN	Any	None
			Moderate	>1.5 - 3 x ULN	Any	Reduce dose to 0.7mg/m^2 in the first treatment cycle. Consider dose escalation to 1mg/m^2 or further dose reduction to 0.5mg/m^2 in subsequent cycles based on patient tolerability.
			Severe	> 3 x ULN	Any	
Thalidomide	Renal impairment: no dose adjustment is needed Haemodialysis: no dose adjustment is needed		Mild and moderate: no dose adjustment is needed Severe: no dose adjustment is needed			
CISplatin	**CrCl (ml/min)**	**Dose**	No need for dose adjustment is expected			
	50-59	75% of the original dose				
	40-49	50% of the original dose				
	<40	Not recommended				
	Haemodialysis	50% of original dose may be conisdered				

Etoposide	**CrCl (ml/min)**	**Dose**	Bilirubin < 50 µmol/L **and** normal albumin **and** normal renal function: no need for dose adjustment is expected Bilirubin ≥ 50 µmol/L **or** decreased albumin levels: consider 50% of the dose, increase if tolerated	
	>50	No dose adjustment needed		
	10-50	75% of the original dose, increase if tolerated		
	Haemodialysis	Not dialysed, consider 75% of the original dose		
DOXOrubicin	**CrCl (ml/min)**	**Dose**	**Bilirubin (micromol/L)**	**Dose**
	>10	No dose adjustment is needed	20-50	50% of the original dose
	<10	No need for dose adjustment is expected	51-86	25% of the original dose
	Haemodialysis	75% of the original dose may be considered	>86 or Child-Pugh C	Not recommended
cycloPHOSphamide	**CrCl (ml/min)**	**Dose**	Mild and moderate: no need for dose adjustment is expected. Severe: not recommended, due to risk of reduced efficacy	
	≥30	No dose adjustment is needed		
	10-29	Consider 75% of the original dose		
	<10	Not recommended, if unavoidable consider 50% of the original dose		
	Haemodialysis	Not recommended, if unavoidable consider 50% of the original dose		
Bortezomib – Renal: Giraud et al 2023, hepatic: SPC. Thalidomide – Renal and hepatic: Giraud et al 2023. CISplatin – Renal and hepatic: Giraud et al 2023. Etoposide – Renal and hepatic: Giraud et al 2023. DOXOrubicin – Renal and hepatic: Giraud et al 2023. cycloPHOSphamide – Renal and hepatic: Giraud at al 2023.				

*Based on NCI Organ Dysfunction Working Group classification for categorising hepatic impairment (mild, moderate, severe).

Management of adverse events:

Table 2: Recommended dose modifications for neuropathy

Drug	Severity of neuropathy*	Dose Modification
Bortezomib	Grade 1(asymptomatic; loss of deep tendon reflexes or paresthesia) with no pain or loss of function	None
	Grade 1 with pain or Grade 2 (moderate symptoms; limiting instrumental activities of daily living (ADL))	Reduce dose to 0.7 mg/m^2 or Change treatment schedule to 1.0mg/m^2 once every week
	Grade 2 with pain or Grade 3 (severe symptoms; limiting self care ADL)	Withhold treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate treatment and reduce dose to 0.7mg/m^2 once every week
	Grade 4 (life-threatening consequences; urgent intervention indicated) and/or severe autonomic neuropathy	Discontinue treatment
Thalidomide	Grade 2 and above	Thalidomide should be stopped if there are symptoms of peripheral neuropathy causing pain or functional disability (grade 2 or above). If symptoms resolve to grade 1 or better (or back to normal baseline) cautious reintroduction at a dose of 50mg should be considered, escalating in 50mg increments as symptoms permit

* Grading based on NCI Common Toxicity Criteria CTCAE v 5.0

Dose reductions for other toxicities:

Table 3: Dose modification schedule based on adverse events

Drug	Adverse reactions*	Recommended dose modification
Bortezomib	Grade ≥3 Non-haematological toxicity	Withhold bortezomib until symptoms resolved to Grade 1 or baseline then reinitiate with one dose level reduction from 1.0mg/m^2 to 0.7mg/m^2. If the toxicity is not resolved or if it recurs at the lowest dose, discontinuation of bortezomib must be considered unless the benefit of treatment clearly outweighs the risk.
	New or worsening pulmonary symptoms (e.g. cough, dyspnoea)	Withhold treatment. Prompt diagnostic evaluation required and benefit/risk ratio should be considered prior to continuing bortezomib therapy.
	Posterior Reversible Encephalopathy Syndrome (PRES)	Discontinue bortezomib
Thalidomide	Angioedema,	Discontinue thalidomide
	Skin rash	Withhold treatment and evaluate clinically. If allergic reaction do not resume treatment.

	Thromboembolic Event	Withhold treatment and start standard anticoagulant therapy. Once stabilised on the anticoagulant therapy and complications of thromboembolic event have been managed, thalidomide treatment may be restarted at the original dose dependant on a benefit/risk assessment. Anticoagulant therapy should be continued during the course of thalidomide treatment.

*Grading based on NCI Common Toxicity Criteria CTCAE v 5.0

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic AntiCancer Therapy (SACT) Induced Nausea and Vomiting linked here

Thalidomide: Minimal to low (**Refer to local policy).**
CISplatin: High (**Refer to local policy).**
Etoposide: Low (**Refer to local policy).**
Bortezomib: Low (**Refer to local policy).**
DOXOrubicin/cycloPHOSphamide: High (**Refer to local policy).**

For information:

Within NCIS regimens, antiemetics have been standardised by Medical Oncologists and Haemato-oncologists and information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - link here
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - link here

PREMEDICATIONS:

- Hydration prior to CISplatin administration **(Refer to local policy or see recommendations above).**

OTHER SUPPORTIVE CARE:

- Patients should have an increased fluid intake of 2-3 litres on day 1 to prevent haemorrhagic cystitis associated with cycloPHOSphamide.
- Bisphosphonates should be considered in all patients with myeloma related bone disease.
- Consider the use of a H_2 antagonist or proton pump inhibitor if appropriate in patients receiving dexamethasone therapy **(Refer to local policy).**
- Tumour Lysis Syndrome prophylaxis **(Refer to local policy).**
- Antiviral prophylaxis **(Refer to local policy).**
- Consider PJP prophylaxis **(Refer to local policy).**
- Prophylactic laxatives to prevent thalidomide induced constipation **(Refer to local policy).**

- Thromboprophylaxis **(Refer to local policy).**
- Influenza vaccination in appropriate patients.
- Male patients must use condoms during treatment with thalidomide, during dose interruption and for at least 7 days following discontinuation of treatment if their partner is pregnant or is of childbearing potential not using effective contraception. Male patients should not donate semen or sperm during treatment (including during dose interruptions) and for at least 7 days following discontinuation of thalidomide.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

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

- **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **Hypersensitivity:** Hypersensitivity reactions have been reported with etoposide and CISplatin. Monitor infusion of etoposide for the first 15 minutes for signs of hypotension.
- **Tumour Lysis Syndrome:** Patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.
- **Hepatitis B Reactivation:** Patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with anti-viral therapy **(Refer to local infectious disease policy)**. These patients should be considered for assessment by hepatology.

Thalidomide

- **Teratogenicity:** Thalidomide must never be used by women who are pregnant or by women who could become pregnant unless all the conditions of the Thalidomide Pregnancy Prevention Programme are met. These conditions must be fulfilled for all male and female patients.
- **Venous and arterial thromboembolic events:** There is an increased risk of venous and arterial thromboembolism in patients treated with thalidomide particularly during the first 5 months of therapy. Previous history of thromboembolic events may also increase thromboembolic risk in these patients. Thromboprophylaxis should be considered especially in patients with additional thrombotic risk factors.
- **Allergic reactions and severe skin reactions**: Cases of allergic reactions including angioedema, anaphylactic reaction and severe cutaneous reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported with the use of Thalidomide. Patients should be advised of the signs and symptoms of these reactions by their prescribers and should be told to seek medical attention immediately if they develop these symptoms. Thalidomide interruption or discontinuation should be considered for Grade 2-3 skin rash. Thalidomide must be discontinued for angioedema, anaphylactic reaction, Grade 4 rash, exfoliative or bullous rash, or if SJS, TEN or DRESS is suspected, and should not be resumed following discontinuation for these reactions.
- **Somnolence:** Patients should be monitored and dose reduction may be required.

CISplatin

- **Renal Toxicity**: Nephrotoxicity is common with CISplatin. Strongly encourage oral hydration. If oral hydration is not possible (e.g. excessive nausea), IV hydration is indicated. Avoid nephrotoxic drugs such as aminoglycoside antibiotics where possible. Where treatment with nephrotoxic drugs must be used, monitor renal function.
- **Ototoxicity and sensory neural damage**: These are associated with CISplatin therapy. They should be assessed by history prior to each cycle.

DOXOrubicin

- **Extravasation**: DOXOrubicin may cause pain and tissue necrosis if extravasated **(Refer to local extravasation guidelines).**
- **Cardiac Toxicity**: DOXOrubicin is cardiotoxic and must be used with caution, if at all, in patients with severe hypertension or cardiac dysfunction.

Bortezomib

- **Haematological toxicity:** Gastrointestinal and intracerebral haemorrhage have been reported in association with bortezomib treatment. Therefore platelet counts should be monitored prior to each dose of bortezomib and bortezomib should be withheld when the platelet count is < 25,000/microliter. Potential benefit of treatment should be carefully weighed against the risks, particularly in case of moderate to severe thrombocytopenia and risk factors for bleeding. Complete blood counts with differential and including platelet counts should be frequently monitored throughout treatment with bortezomib. Platelet transfusion should be considered when clinically appropriate.
- **Progressive multifocal leukoencephalopathy (PML):** Patients should be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML as part of the differential diagnosis of CNS problems. If a diagnosis of PM is suspected patients should be referred to a specialist in PML and appropriate diagnostic measures for PML should be initiated. Discontinue bortezomib if PML is diagnosed.
- **Peripheral Neuropathy:** Patients with pre-existing severe neuropathy may be treated with bortezomib only after careful risk/benefit assessment.
- **Seizures:** Seizures have been uncommonly reported in patients without previous history of seizures or epilepsy. Special care is required when treating patients with any risk factors for seizures.
- **Hypotension**: Treatment is commonly associated with orthostatic/postural hypotension. A minority of patients with orthostatic hypotension experienced syncopal events. Caution is advised when treating patients with a history of syncope receiving medicinal products known to be associated with hypotension; or who are dehydrated due to recurrent diarrhoea or vomiting.
- **Posterior Reversible Encephalopathy Syndrome (PRES):** In patients developing PRES, treatment with bortezomib should be discontinued.
- **Heart Failure**: Acute development or exacerbation of congestive heart failure, and/or new onset of decreased left ventricular ejection fraction has been reported during bortezomib treatment. Patients with risk factors for or existing heart disease should be closely monitored.
- **Renal Impairment:** Patients with renal impairment should be monitored closely.
- **Hepatic Impairment;** Bortezomib is metabolised by liver enzymes. Bortezomib exposure is increased in patients with moderate or severe hepatic impairment; these patients should be

treated with bortezomib at reduced doses and closely monitored for toxicities.

- **Gastrointestinal toxicity:** Gastrointestinal toxicity, including nausea, diarrhoea, vomiting and constipation are very common with bortezomib treatment

dexAMETHasone

- **Steroid use:** Steroid use is associated with numerous side effects including insomnia, gastric irritation, increased blood sugar levels, mood changes, increased appetite, bruising, skin fragility and osteoporosis (long term use).

DRUG INTERACTIONS:

- CISplatin may potentiate the nephrotoxic and ototoxic effects of loop diuretics and aminoglycosides so concurrent use should be avoided.
- Concomitant CISplatin therapy is associated with reduced total body clearance of etoposide.
- CYP3A4 inducers may increase the clearance of etoposide. CYP3A inducers may also increase the conversion of cyclophosphamide to both its active and inactive metabolites.
- CYP3A4 and p-gp inhibitors may decrease the clearance of etoposide. CYP3A inhibitors decrease the conversion of cyclophosphamide to both its active and inactive metabolites. Patients should also be counselled with regard to consumption of grapefruit juice.
- Concurrent administration of calcium channel blockers with DOXOrubicin should be avoided as they may decrease the clearance of DOXOrubicin.
- Additive hypotensive effect with antihypertensives and bortezomib. Blood pressure should be monitored and ensure patient is well hydrated prior to bortezomib dose. Adjustment of antihypertensives may be required.
- During clinical trials, hypoglycemia was uncommonly reported and hyperglycemia commonly reported in diabetic patients receiving oral hypoglycemics. Patients on oral antidiabetic agents receiving bortezomib treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetics
- Patients should be closely monitored when given bortezomib in combination with potent CYP3A4-inhibitors. Caution should be exercised when bortezomib is combined with CYP3A4- or CYP2C19 substrates.
- Thalidomide may enhance the sedation induced by anxiolytics, hypnotics, antipsychotics, H1 anti-histamines, opiate derivatives, barbiturates and alcohol.
- Due to thalidomide's potential to induce bradycardia, caution should be exercised with medicinal products having the same pharmcodynamic effect such as active substances known to induce torsade de pointes, beta blockers or anticholinesterase agents.
- Current drug interaction databases should be consulted for more information.

COMPANY SUPPORT RESOURCES/Useful Links:

Please note that this is for information only and does not constitute endorsement by the NCCP

Thalidomide

- Please refer to the HPRA website (www.hpra.ie) for the individual product for list of relevant support resources
- Prescribers are required to read and understand the relevant HCP Information Guide and to adhere to the PPP

REFERENCES:

1. Lee C-K et al. DTPACE: an effective, novel combination chemotherapy with thalidomide for previously treated patients with myeloma. J Clin Oncol. 2003; 21:2732-2739.
2. Barlogie B et al. Incorporating bortezomib into upfront treatment for multiple myeloma: early results of total therapy 3. British Journal of Haematology 2007; 138(2): 176-185
3. Giraud EL, de Lijster B, Krens SD, Desar IME, Boerrigter E, van Erp NP. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Lancet Oncol 2023; 24: e229.
4. 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
5. CISplatin Summary of Product Characteristics HPRA. Last updated: 14/03/2023. Accessed Dec 2023 Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0822-199-001_14032023145612.pdf
6. Etoposide 20 mg/ml Concentrate for Solution for Infusion Summary of Product Characteristics. HPRA Last updated: 17/05/2021. Accessed Dec 2023. Available at: http://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2059-036-001_17052021114619.pdf
7. DOXOrubicin 2mg/ml Concentrate for Solution for Infusion. Summary of Product Characteristics. Last updated Feb 2020. Accessed Dec 2023. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2315-083-001_26022020112618.pdf
8. cycloPHOSphamide (Endoxana®) Injection 500mg Powder for Solution for Injection. Summary of Product Characteristics. Last updated Dec 2021. Accessed Dec 2023. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2299-027-001_21122018112107.pdf
9. Bortezomib (Velcade®)Summary of Product Characteristics. Accessed Dec 2023. Available at: https://www.ema.europa.eu/en/documents/product-information/velcade-epar-product-information_en.pdf
10. Thalidomide BMS Summary of Product Characteristics. Accessed Dec 2023. Available at: https://www.ema.europa.eu/en/documents/product-information/thalidomide-bms-previously-thalidomide-celgene-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	01/07/2024		Dr Amjad Hayat

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This is an unlicensed indication for the use of bortezomib 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

[ii] Cardiotoxicity is a risk associated with anthracycline therapy that may be manifested by early (acute) or late (delayed) effects.

Risk factors for developing anthracycline-induced cardiotoxicity include:

• high cumulative dose, previous therapy with other anthracyclines or anthracenediones

• prior or concomitant radiotherapy to the mediastinal/pericardial area

• pre-existing heart disease

• concomitant use of other potentially cardiotoxic drugs