Gemcitabine 1000mg/m^2, Vinorelbine 20mg/m^2 and Pegylated Liposomal DOXOrubicin 15mg/m^2 (GVD) Therapy – Transplant Naive

- **Note: This regimen is for treatment of transplant naïve patients only. For treatment of post-transplant patients, please refer to NCCP regimen 895 Gemcitabine 800mg/m^2, Vinorelbine 15mg/m^2 and Pegylated DOXOrubicin 10mg/m^2 (GVD) Therapy – Post transplant.**
- **Please note that the Myocet® product, which contains non-pegylated liposomal DOXOrubicin should not be used when treating patients with this regimen.**

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Treatment of relapsed or refractory Hodgkin's lymphoma in transplant naïve patients[i]	C81	00853a	N/A

* This applies to post 2012 indications

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 patient's individual clinical circumstances.

Treatment is administered on day 1 and day 8 of a 21-day cycle 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, 8	Vinorelbine[a]	20mg/m^2	IV infusion	50mL NaCl 0.9% over 15 minutes. Then flush the line with 250mL NaCl 0.9% prior to removing/capping IV access.	Every 21 days
1, 8	Gemcitabine	1000mg/m^2	IV infusion	250mL NaCl 0.9% over 30 minutes	Every 21 days
1, 8	Pegylated liposomal DOXOrubicin[b]	15mg/m^2	IV infusion	250mL[c] glucose 5% at rate of 1mg/minute for first cycle (see note)	Every 21 days

[a]Vinorelbine is a neurotoxic chemotherapeutic agent.

Refer to NCCP Guidance on the Safe Use of Neurotoxic drugs (including Vinca Alkaloids) in the treatment of cancer https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/safetyreview/neurotoxicguidance.pdf

[b]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** The evaluation of LVEF is considered to be mandatory before each additional administration of pegylated liposomal DOXOrubicin that exceeds a lifetime cumulative anthracycline dose of 450mg/m^2. Cardiac toxicity also may occur at cumulative anthracycline doses lower than 450mg/m^2 in patients with prior mediastinal irradiation or in those receiving concurrent cyclophosphamide therapy.
[c]For doses ≥ 90mg, use 500mL infusion bag Do not use with in-line filters **NOTE**: If no infusion reaction observed subsequent infusions may be administered over 60min. For patients who experience an infusion reaction, the method of infusion should be modified as follows: 5% of the total dose should be infused slowly over the first 15 minutes. If tolerated without reaction, the infusion rate may then be doubled for the next 15 minutes. If tolerated, the infusion may then be completed over the next hour for a total infusion time of 90 minutes.

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

ELIGIBILITY:

- Indication as above
- Eligible for stem cell transplant
- ECOG 0-3
- In patients with lifetime cumulative dose of DOXOrubicin >400mg/m^2, LVEF must be ≥45%
- Adequate renal, hepatic and haematological function

EXCLUSIONS:

- Hypersensitivity to gemcitabine, vinorelbine, pegylated liposomal DOXOrubicin, peanut, soya or any of the excipients
- Pre-existing cardiac myopathy or congestive heart failure
- Hepatic dysfunction (see Dose Modifications below)
- Pregnancy
- Breastfeeding

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Serology for Hepatitis B (HBV), [HBV sAg, HBV sAb, HBV cAb], hepatitis C (HCV), human immunodeficiency virus (HIV), cytomegalovirus (CMV) [IgG] and EBV
    - Reference Regimen Specific Complications for information on Hepatitis B reactivation
- Assessment of peripheral neuropathy status if clinically indicated
- ECG
- MUGA or ECHO
    - See Regimen Specific Complications for guidelines regarding cardiotoxicity

Regular tests:

- FBC prior to each treatment on day 1 and 8
- Renal and liver profile
- Assessment of peripheral neuropathy status if clinically indicated
- ECG
- MUGA or ECHO as clinically indicated

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:

Table 1: Dose modification in haematological toxicity on Day 1

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose (all drugs)
≥1.0	and	≥75	100%
<1.0	or	<75	Delay until recovery

Table 2: Dose modification in haematological toxicity on Day 8

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose (all drugs)
≥1.0	and	≥75	100%
0.5 – 0.99	and	50 - 74	Reduce gemcitabine and vinorelbine dose to 75% of current cycle's day 1 dose; give 100% dose of pegylated liposomal DOXOrubicin
<0.5	or	<50	Omit

Renal and Hepatic Impairment:

Table 3: Dose modification in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment	
Gemcitabine	**CrCl (mL/min)**	**Dose**	**Total Bilirubin (micromol/L)**	**Dose**
	≥30	No dose adjustment is needed	<27	No dose adjustment is needed
	<30	No need for dose adjustment is expected		
	Haemodialysis	No need for dose adjustment is expected. Start haemodialysis 6-12 hours after administration	≥27	Either start at 80% of original dose and increase the dose if tolerated, **OR** start with full dose with active monitoring
Vinorelbine	No dose adjustment is needed Haemodialysis: No need for dose adjustment is expected		**Mild/Moderate**	No dose adjustment is needed
			Severe (Total bilirubin >3xULN, any ALT/AST)	Consider 66% of original dose
Pegylated liposomal DOXOrubicin	No need for dose adjustment is expected Haemodialysis: No need for dose adjustment is expected		**Total Bilirubin (micromol/L)**	**Dose**
			20-50	75% of original dose
			51-86	50% of original dose
			>86	Not recommended
Renal and hepatic dose modifications: Giraud et al 2023				

Management of adverse events:

Table 4: Dose Modification of pegylated liposomal DOXOrubicin for Palmar-Plantar Erythrodysesthesia (PPE) and Stomatitis

Toxicity Grade at Current Assessment	Day 1 of new cycle	Delayed one week	Delayed 2 weeks
Grade 1	**Proceed with dose unless** patient has experienced a previous Grade 3 or 4 skin toxicity or stomatitis, in which case delay 1 week	**Proceed with dose unless** patient has experienced a previous Grade 3 or 4 skin toxicity or stomatitis, in which case delay another week	PPE and stomatitis: Decrease dose by 25 %; **OR** Stomatitis: Consider discontinuation - clinician decision
Grade 2	Delay 1 week	Delay an additional week	PPE and stomatitis: Decrease dose by 25 %; **OR** Stomatitis: Consider

			discontinuation - clinician decision
Grade 3	Delay 1 week	Delay an additional week	Discontinue
Grade 4	Delay 1 week	Delay an additional week	Discontinue

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic AntiCancer Therapy (SACT) Induced Nausea and Vomiting available on NCCP website

Gemcitabine: Low **(Refer to local policy).**
Vinorelbine: Minimal **(Refer to local policy).**
Pegylated liposomal DOXOrubicin: Low **(Refer to local policy).**

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

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) available on NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) available on NCCP website

PREMEDICATIONS: None usually required

OTHER SUPPORTIVE CARE:

- Other strategies to prevent and treat PPE, which may be initiated for 4 to 7 days after treatment with pegylated liposomal DOXOrubicin include keeping hands and feet cool, by exposing them to cool water (soaks, baths, or swimming), avoiding excessive heat/hot water and keeping them unrestricted (no socks, gloves, or shoes that are tight fitting) (**Refer to local policy**).
- Prophylactic regimen against vinorelbine-induced constipation is recommended, grade 1-2 can be managed with dietary interventions or laxatives **(Refer to local policy).**
- Anti-viral prophylaxis **(Refer to local policy).**
- PJP prophylaxis **(Refer to local policy).**

ADVERSE EFFECTS:

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details.

REGIMEN SPECIFIC COMPLICATIONS:

- **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.
- **Cardiotoxicity**: Frequent ECG monitoring is recommended. Reduction of the QRS complex suggests cardiac toxicity. LVEF monitoring using ECHO or MUGA should be applied during treatment.
- **Palmar-plantar erythrodysesthesia syndrome (PPE):** Monitor patient for presence of PPE. If present, patient may require an interruption in treatment (see dose modifications).
- **Pulmonary Toxicity**: Acute shortness of breath may occur. Discontinue treatment if drug-induced pneumonitis is suspected.
- **Cardiovascular:** Due to the risk of cardiac and/or vascular disorders with gemcitabine, particular caution must be exercised with patients presenting a history of cardiovascular events.
- **Irreversible renal failure** associated with haemolytic uraemic syndrome may occur rarely with gemcitabine. Use caution with pre-existing renal impairment.
- **Extravasation:** Vinorelbine is a vesicant and causes pain and tissue necrosis if extravasated (Refer to local guidelines). Pegylated liposomal DOXOrubicin is considered an irritant (Refer to local policy).
- **Peripheral neuropathy:** This can occur as a side effect in patients treated with this regimen. Early detection of and intervention for peripheral neuropathy is associated with improved quality of life and outcomes for patients. Regular assessment for signs and symptoms should be carried out as per the testing section of this regimen.

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information.

REFERENCES:

1. Barlett N.L, et al. Gemcitabiine, vinorelbine, and pegylated liposomal doxorubicin (GVD), a salvage regimen in relapsed Hodgkin's lymphoma: CALGB 59804. Ann Oncol. 2007; 18(6): 1071-9.
2. 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/
3. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V6 2025. 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
4. Gemcitabine Summary of Product Characteristics. Accessed Nov 2024. Available at: https://assets.hpra.ie/products/Human/27418/Licence_PA1986-122-001_14122023101810.pdf
5. Pegylated liposomal DOXOrubicin (Caelyx pegylated liposomal®) Summary of product characteristics. Accessed Nov 2024. Available at:

https://www.ema.europa.eu/en/documents/product-information/caelyx-pegylated-liposomal-epar-product-information_en.pdf

6. Vinorelbine (Navelbine®) Summary of Product Characteristics available from NCCP upon request.

Version	Date	Amendment	Approved By
1	14/07/2025		Dr Robert Henderson

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This is an unlicensed indication for the use of gemcitabine, vinorelbine and pegylated liposomal DOXOrubicin 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