Escalated Dose BEACOPP 21 day Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Treatment of patients with high risk, advanced stage Hodgkin Lymphoma (IPS ≥ 3)	C81	00354a	N/A
Escalation of treatment of patients with Hodgkin Lymphoma after failure to reach complete metabolic response post 2 cycles of ABVD	C81	00354b	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.

The treatment is administered every 21 days for 4 cycles unless disease progression or unacceptable toxicity develops. This can be increased to 6 cycles at the consultant's discretion.
Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Day	Drug	Dose	Route	Diluent and Rate
1	[a]cycloPHOSphamide	1250mg/m^2	IV infusion	250mL NaCl 0.9% over 30 minutes
1	[b]DOXOrubicin	35mg/m^2	IV Bolus	Slow IV bolus over 15 minutes with NaCl 0.9%
1,2,3	[c]Etoposide	200mg/m^2	IV infusion	1000mL NaCl 0.9% over 3 hours
8	[d]vinCRIStine	1.4mg/m^2 (cap at 2mg)	IV infusion	50mL NaCl 0.9% over 15 minutes
8	[e]Bleomycin	10,000IU International units/ m^2	IV Bolus	Into the side arm of a fast running NaCl 0.9% infusion
1-7	[f]Procarbazine	100mg/m^2 once daily	PO	
1-14	[g]prednisoLONE	40mg/m^2 once daily	PO	
9-13 approx.	G-CSF (Round to nearest whole syringe)	5 micrograms/kg	SC	until ANC >1x10^9/L for 3 days
[a]Consideration could be given to the administration of MESNA 250mg/m^2 IV at T0, T+4 and T+8hr after administration of the cycloPHOSphamide at the discretion of the prescribing consultant.				
[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[i] and to the age of the patient.**				
[c] The etoposide 200mg/m^2 dose may need to be split into two 1000mL bags for stability reasons. These should be administered sequentially.				
[d]vinCRIStine is a neurotoxic chemotherapeutic agent. Refer to NCCP Guidance on the Safe Use of Neurotoxic drugs (including Vinca Alkaloids) in the				

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treatment of cancer Available on the NCCP website .
[e] Lifetime cumulative dose of bleomycin is 400,000 international units (Bleomycin has been associated with severe and life threatening respiratory complications. The total cumulative dose of bleomycin should NOT exceed 400,000 international units. The risk of pulmonary toxicity increases beyond acumulative dose of 300,000 international units. Check the cumulative dose prior to each treatment) Bleomycin dosing should only be expressed in terms of international units.
[f]Procarbazine is an unlicensed drug. If the drug is not to be dispensed by the hospital, then the hospital should ensure communication with the patient's community pharmacy to ensure there is no interruption in treatment. Procarbazine is commonly available as 50mg capsules, round dose to nearest 50mg.
[g]Alternative steroid regimens with tapering doses may be used at consultant discretion, **e.g.** 60mg od for 14 days, 40mg od for 2 days, 20mg od for 2 days, 15mg od for 1 day, 10mg od for 1 day, 5mg od for 1 day-,then, stop* (21 days in total) prednisoLONE is taken as a single daily dose in the morning.

ELIGIBILITY:

- Indications as above
- ECOG status 0-2

EXCLUSIONS:

- Hypersensitivity to cycloPHOSphamide , DOXOrubicin, , etoposide, vinCRIStine, bleomycin procarbazine, prednisoLONE or any of the excipients.
- Age ≥ 60 years
- Bleomycin is contraindicated in patients with acute pulmonary infection or chest X rays suggesting diffuse fibrotic changes or greatly reduced lung function
- Severe liver impairment (etoposide)
- Breast feeding
- Pregnancy

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- ECG
- Cardiac function using MUGA or ECHO (LVEF > 50% required to administer doxorubicin) if >65 years or if clinically indicated (e.g. smoking history, hypertension).
- Pulmonary function tests (PFTs) prior to bleomycin
- Virology screen - Hepatitis B (HBsAg, HBcoreAb), Hepatitis C, HIV
  *See Adverse Effects/Regimen Specific Complications re Hepatitis B Reactivation

Regular tests:

- FBC, renal and liver profile prior to each cycle on day 1
- Chest x-ray +/- PFTs, 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.

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DOSE MODIFICATIONS:

- Full dose intensity should be maintained where possible.
- Dose modification should only be carried out following discussion and approval by the consultant.

Haematological:

Table 1: Haematological Criteria to proceed with next cycle of treatment

	White Cell Count		Platelets	Recommendation
Day 1	>2.5 X 10^9/L	and	> 80 X 10^9/L	Cycle proceeds

- If these values are not reached on day 1 of the next scheduled cycle of treatment, therapy is postponed and FBC should be checked again after 3, 7, 10 and 14 days or until blood count recovery.
- Bleomycin and vinCRIStine should be administered on schedule and at full dose even if leucopenia is observed on day 8.

Dose modifications (De-escalation as per HD15 protocol, Engert et al)

There is a predefined scheme for dose de-escalation for BEACOPP Escalated Therapy.

Ensure to discuss with consultant prior to implementing dose modifications as dose intensity should be maintained where possible

- The dose in all subsequent cycles will be reduced by one dose level should one or more toxic events occur in a given cycle (see Table 2 below).
- If any toxic event occurs in 2 successive cycles, the subsequent cycle is administered at baseline dose.
- Once dose levels have been reduced, they are not re-escalated for subsequent cycles.

Consider requirement for dose reduction (as per Table 2 below) for the following toxic events.

Toxic events include:

- Grade 4 neutropenia or thrombocytopenia
- Grade 4 leucopenia for more than 4 days (White cell count < 1 x 10^9/L)
- Other grade 4 toxicity

Table 2: Dose reduction levels for Escalated BEACOPP

Level	cycloPHOSphamide (Day 1)	DOXOrubicin (Day 1)	Etoposide (Day 1-3)
*4	1250 mg/m^2	35 mg/m^2	200 mg/m^2
3	1100 mg/m^2	35 mg/m^2	175 mg/m^2
2	950 mg/m^2	35 mg/m^2	150 mg/m^2
1	800 mg/m^2	35 mg/m^2	125 mg/m^2
Baseline	650 mg/m^2	25 mg/m^2	100 mg/m^2

*Starting Level

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Renal and Hepatic Impairment:

Table 3: Recommended dose modifications based on renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment			
cycloPHOSphamide	**CrCl (mL/min)**	**Dose**	Severe impairment: Clinical decision			
	>20	100%				
	10-20	75%				
	<10	50%				
Bleomycin	**CrCl (mL/min)**	**Dose**	Clinical decision			
	>50	100%				
	10-50	75%				
	<10	50%				
DOXOrubicin	No dose reduction required. Clinical decision in severe renal impairment.		**Bilirubin (micromol/L)**	**Dose**		
			20-51	50%		
			51-85	25%		
			>85	omit		
			If AST 2-3x normal, give 75% dose. If AST >3x ULN, give 50% dose.			
Etoposide	**CrCl (mL/min)**	**Dose**	**Bilirubin (micromol/L)**		**AST**	**Dose**
	>50	100%	26-51	or	60-180	50%
	15-50	75%	>51	or	>180	Clinical decision
	<15	50%				
	Subsequent doses should be based on clinical response					
Procarbazine	Caution is advisable in patients with renal dysfunction. Avoid use if creatinine clearance is less than 10mL/min		**Bilirubin (micromol/L)**		**AST**	**Dose**
			>50			Consider dose reduction
			>85	or	>180	Contraindicated
vinCRIStine	No dose reduction required		**Bilirubin (micromol/L)**		**AST/ALT**	**Dose**
			26-51	or	60-180	50%
			>51	and	Normal	50%
			>51	and	>180	Omit
			Consider if liver impairment is disease related			

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Neurotoxicity:

Table 4: Dose modification of vinCRIStine based on neurotoxicity (CTCAE v 4.0)

Peripheral neuropathy	Dose of vinCRIStine
Grade 1	100%
Grade 2	Hold until recovery, then reduce dose by 50
Grade 3,4	Omit

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

As outlined in NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting - Available on the NCCP website

cycloPHOSphamide: Moderate **(Refer to local policy)**
DOXOrubicin: Moderate **(Refer to local policy)**
Etoposide: Low **(Refer to local policy)**
Procarbazine: Moderate to High **(Refer to local policy)**
vinCRIStine: Minimal **(Refer to local policy)**
Bleomycin: Minimal **(Refer to local policy)**

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) - Available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for Inclusion in NCIS (Haemato-oncology) - Available on the NCCP website

PREMEDICATIONS:

None usually required

OTHER SUPPORTIVE CARE:

- Tumour lysis syndrome prophylaxis **(Refer to local policy)**
- Proton pump Inhibitor **(Refer to local policy)**
- PJP prophylaxis **(Refer to local policy)**
- Anti-viral prophylaxis **(Refer to local policy)**
- Anti-fungal prophylaxis (Avoid the concurrent use of azoles and vinCRIStine **(Refer to local policy)**
- Prophylactic regimen against vinCRIStine induced constipation is recommended **(Refer to local policy)**
- Patients should have an increased fluid intake of 2-3 litres on day 5 to prevent haemorrhagic cystitis associated with cycloPHOSphamide.
- All patients should receive irradiated blood products – **Refer to local policy** for notification procedure
- Consider referral for fertility preservation

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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.
- **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.
- **Extravasation:** vinCRIStine and DOXOrubicin causes pain and possible tissue necrosis if extravasated **(Refer to local policy)**.

DOXOrubicin

- **Cardiotoxicity:** DOXOrubicin is cardiotoxic and must be used with caution, if at all, in patients with severe hypertension or cardiac dysfunction.

vinCRIStine

- **Neuropathy:** vinCRIStine may cause peripheral neuropathy, which is dose related and cumulative, requiring monitoring before each dose is administered. The presence of pre-existing neuropathies or previous treatment with other neurotoxic drugs may increase risk of peripheral neuropathy. Patients with mild peripheral neuropathy can usually continue to receive full doses of vinCRIStine, but when symptoms increase in severity and interfere with neurologic function, dose reduction or discontinuation of the drug may be necessary. The natural history following discontinuation of treatment is gradual improvement, which may take up to several months.
- **Constipation:** A routine prophylactic regimen against constipation is recommended for all patients receiving vinCRIStine sulphate. Paralytic ileus may occur. The ileus will reverse itself upon temporary discontinuance of vinCRIStine and with symptomatic care.

Bleomycin

- **Pulmonary toxicity**: Bleomycin may cause severe and life threatening pulmonary toxicity. Pulmonary toxicity of bleomycin is both dose-related and age-related. It may also occur when lower doses are administered, especially in elderly patients; in patients with reduced kidney function, pre-existing lung disease, previous or concurrent radiotherapy to the chest and in patients who need administration of oxygen. It is significantly exacerbated by thoracic radiation and by hyperoxia used during surgical anaesthesia. Smoking is also a risk factor.

DRUG INTERACTIONS:

- Procarbazine is a weak MAO inhibitor and therefore, interactions with certain foodstuffs and drugs, although very rare, can occur. Thus, owing to possible potentiation of the effect of barbiturates, narcotic analgesics (especially pethidine), drugs with anticholinergic effects (including phenothiazine derivatives and tricyclic antidepressants), other central nervous system depressants (including anaesthetic agents) and anti-hypertensive agents, these drugs should be given concurrently with caution and in low doses.
- Intolerance to alcohol (Disulfiram-like reaction) may occur with procarbazine.

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- DOXOrubicin cardiotoxicity is exacerbated by previous or concurrent use of other anthracyclines or other potentially cardiotoxic drugs (e.g. 5-Fluorouracil, cycloPHOSphamide or PACLitaxel) or products affecting cardiac function (e.g. calcium antagonists).
- CYP3A4 inducers may increase the clearance of etoposide.
- CYP3A4 and p-gp inhibitors may decrease the clearance of etoposide.
- Bleomycin causes sensitisation of lung tissue to oxygen. If oxygen is required, the use of low concentration (e.g. 25%) is recommended. Fluid replacement should be carefully monitored.
- Current drug interaction databases should be consulted for more information, including potential for interactions with CYP3A4 inhibitors/inducers**.**

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Version	Date	Amendment	Approved By
1	08/03/2019		Dr Hilary O'Leary

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	20/03/2019		Dr Kamal Fadalla Prof Maccon Keane
2	23/04/2020	Updated treatment table footnotes for etoposide administration, updated dose modifications for cyclophosphamide in hepatic impairment	Prof Maccon Keane
3	14/10/2022	Reviewed. Amended Treatment Table (Removed reference to bleomycin mg dosing). Updated exclusions, emetogenic potential and adverse effects. Updated drug interactions.	Prof Maccon Keane
3a	13/01/2025	Amended heading in Table 2. Added links in emetogenic potential section.	NCCP
3b	20/11/2025	Updated footnote in treatment table regarding cumulative doses.	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] 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
In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors above and to the age of the patient

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