ABVD Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*Reimbursement Status
Hodgkin's Lymphoma	C81	00290a	Hospital

**If the reimbursement status is not defined [i], the indication has yet to be assessed through the formal HSE reimbursement process.*

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 on day 1 and day 15 of a 28 day treatment cycle for a maximum of 6-8 cycles or until disease progression or unacceptable toxicity develops.

Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered.

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1,15	[a]DOXOrubicin	25mg/m^2	IV Bolus	Into the side arm of a fast running 0.9% NaCl infusion	Every 28 days for a maximum of 6-8 cycles
2	1,15	[b]VinBLAStine	6mg/m^2	IV infusion	50ml NaCL 0.9% over 10 min	Every 28 days for a maximum of 6-8 cycles
3	1,15	[c]Dacarbazine	375mg/m^2	IV infusion	[d]250ml 0.9% NaCl over 30min	Every 28 days for a maximum of 6-8 cycles
4	1,15	[e,f]Bleomycin	10,000IU/m^2 (10mg/m^2)	IV Bolus	Into the side arm of a fast running 0.9% NaCl infusion	Every 28 days for a maximum of 6-8 cycles
[a]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 below[ii] and to the age of the patient**						
[b]VinBLAStine is a neurotoxic chemotherapeutic agent. Refer to NCCP Guidance on the Safe Use of Neurotoxic drugs (including Vinca Alkaloids) in the treatment of cancer						
[c]Dacarabazine is sensitive to light exposure. All reconstituted solutions should be suitably protected from light also during administration (light-resistant infusion set)						
[d]Consideration should be given to recommended concentration and stability of product. The volume of infusion should be adjusted appropriately						
[e]Bleomycin dosing may be referred to in IU or in mg. 1,000IU = 1mg.						
[f]Lifetime cumulative dose of bleomycin is 400,000IU (400mg). (Bleomycin has been associated with severe and life threatening respiratory complications. The total cumulative dose of bleomycin should NOT exceed 400,000 international units (400mg). The risk of pulmonary toxicity increases beyond a cumulative dose of 300,000 international units (300mg). Check the cumulative dose prior to each treatment.)						

ELIGIBILTY:

- Indications as above
- ECOG 0-3. Patients with an ECOG 4 may be considered for treatment at the discretion of the treating clinician

EXCLUSIONS:

- Hypersensitivity to DOXOrubicin, bleomycin, vinBLAStine, dacarbazine or any of the excipients.
- Cardiac assessment should be considered prior to the administration of DOXOrubicin in high-risk patients.
- A cumulative life-long dose of 450mg/m^2 of DOXOrubicin should only be exceeded with extreme caution as there is as risk of irreversible congestive heart failure
- Bleomycin is contraindicated in patients with acute pulmonary infection or chest X rays suggesting diffuse fibrotic changes or greatly reduced lung function.

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile, blood glucose.
- ECG
- MUGA or ECHO should be considered prior to the administration of DOXOrubicin in high-risk patients
- Pulmonary Function Tests (PFTs) prior to bleomycin
- Neurotoxicity assessment
- Virology screen -Hepatitis B (HBsAg, HBcoreAb) & C, HIV.
  *See Adverse Effects/Regimen Specific Complications re Hepatitis B Reactivation

Regular tests:

- FBC, renal and liver before day 1 and day 15 of each cycle (day 15 may not be necessary, refer to local policy)
- Neurotoxicity assessment prior to each cycle
- Cardiac function if clinically indicated.
- PFTs if 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:

- Full dose intensity should be maintained irrespective of neutrophil count
- G-CSF should be avoided as this may precipitate bleomycin lung toxicity. Use only following agreement with the treating consultant.
- If platelet count < 75 x 10^9/L treatment may need to be delayed by one week, discuss with consultant

Renal and Hepatic Impairment:

Table 1: Dose modification of ABVD in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment		
DOXOrubicin	Dose reduction may be considered in severe renal impairment –clinical decision.		**Bilirubin (micromol/L)**		**Dose**
			20-51		50%
			51-85		25%
			>85		Omit
			If AST 2-3 x normal, give 75% of dose If AST > 3 ULN give 50% dose		
Bleomycin	**CrCl (ml/min)**	**Dose**	Clinical decision		
	>50	100%			
	10-50	75%			
	<10	50%			
VinBLAStine	No dose reduction necessary		**Bilirubin (micromol/L**	**AST/ALT/units**	**Dose**
			26-51 or	60-180	50%
			>51 and	normal	50%
			> 51 and	>180	omit
Dacarbazine	**CrCl (ml/min)**	**Dose**	Can be hepatotoxic. Consider dose reduction		
	45-60	80%			
	30-45	75%			
	<30	70%			

Management of adverse events:

Table 2: Dose Modification of ABVD for Adverse Events

Adverse reactions	Recommended dose modification
Grade >2 Peripheral neuropathy(vinBLAStine only)	Dose reduction of **vinBLAStine** may be required at the discretion of the prescribing consultant
Bleomycin Induced Pulmonary Toxicity:	Bleomycin should be discontinued in patients demonstrating clinical or radiographic evidence of pulmonary injury or significant deterioration of pulmonary diffusion capacity. **Do not reintroduce bleomycin to patients with any bleomycin-induced lung injury.**

SUPPORTIVE CARE:

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

PREMEDICATIONS: None usually required

OTHER SUPPORTIVE CARE:

- All patients should receive irradiated blood products – refer to local policy for notification procedure
- Tumour lysis syndrome prophylaxis for first cycle **(Refer to local policy)**
- Anti-viral prophylaxis **(Refer to local policy)**
- Mouth care prophylaxis **(Refer to local policy)**

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.
- **Cardiac Toxicity:** DOXOrubicin is cardiotoxic and must be used with caution in patients with a history of cardiac dysfunction
- **Pulmonary Toxicity**: Bleomycin lung toxicity may occur in up to 10- 20% with increased risk in age>40 years, smoking, renal impairment and G-CSF use. Pulmonary toxicity of bleomycin is both dose-related and age-related. It may also occur when lower doses are administered, especially in elderly patients, 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 enhanced by thoracic radiation and by hyperoxia used during surgical anaesthesia.
- All patients complaining of shortness of breath require a CXR and PFTs prior to further administration of bleomycin. Bleomycin should be discontinued if any signs or CXR evidence of pulmonary infiltration/fibrosis develop, or if the transfer factor is <50% of the predicted value. Patients with pulmonary infiltrates should be treated with steroids and broad spectrum antibiotics.
- **Extravasation**: DOXOrubicin and vinBLAStine cause pain and tissue necrosis if extravasated **(Refer to local policy).**
- **Hypersensitivity:** There is a high risk of a hypersensitivity reaction with bleomycin.
- **Hepatitis B Reactivation:** All lymphoma patients should be tested for both HBsAg and HBcoreAb. If either test is positive, such patients should be treated with Lamivudine 100 mg/day orally, for the entire duration of chemotherapy and for six months afterwards. Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA at least every two months. If the hepatitis B virus DNA level rises during this monitoring, management should be reviewed with an appropriate specialist with experience managing hepatitis and consideration given to halting chemotherapy

DRUG INTERACTIONS:

- DOXOrubicin cardiotoxicity is enhanced by previous or concurrent use of other anthracyclines, or other potentially cardiotoxic drugs (e.g. 5-Fluorouracil, cyclophosphamide or PACLitaxel) or with products affecting cardiac function (e.g. calcium antagonists).
- Concomitant use of phenytoin and dacarbazine should be avoided since there is a risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption
- Concomitant use of live-attenuated vaccines should be avoided
- Dacarbazine is metabolised by cytochrome P450 (CYP1A1, CYP1A2 and CYP2E1). This must be taken into account if other medicinal products are co-administered with dacarbazine that are metabolised by the same hepatic enzymes.
- Current drug interaction databases should be consulted for more information

ATC CODE:

DOXOrubicin	-	L01DB01
VinBLAStine	-	L01CA01
Bleomycin	-	L01DC01
Dacarbazine	-	L01AX04

REFERENCES:

1. Evens AM, Cilley J et al. G-CSF is not necessary to maintain over 99% dose-intensity with ABVD in the treatment of Hodgkin lymphoma:low toxicity and excellent outcomes in a 10-year analayis. Br J Haem 2007; 137 (6):545-552
2. Gobbi PG, Levis A, Chisesi T, et al. ABVD versus modified stanford V versus MOPPEBVCAD with optional and limited radiotherapy in intermediate- and advanced-stage Hodgkin's lymphoma: final results of a multicenter randomized trial by the Intergruppo Italiano Linfomi. J Clin Oncol 2005; 23(36):9198-207. Epub 2005 Sep 19.
3. Canellos GP et al. Long term follow up of Hodgkins disease trial. NEJM 2002;346 (18):1417-1418.
4. Canellos GP et al. Chemotherapy of Advanced Hodgkin's Disease with MOPP, ABVD, or MOPP Alternating with ABVD NEJM 1992; 327(21): 1478-1484
5. The North London Cancer Network, Dose adjustment for cytotoxics in hepatic impairment, Jan 2009.
6. DOXorubicin Summary of Product Characteristics Accessed Nov 2018. Available at: https://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA1380-111-001_19012018092038.pdf
7. Vinblastine Summary of Product Characteristics Accessed Nov 2018 Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0822-208-001_31102018125148.pdf
8. Dacarbazine Summary of Product Characteristics Accessed Nov 2018. Availble at: https://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA0623-003-002_15032017132108.pdf
9. Bleomycin Summary of Product Characteristics Accessed Nov 2018. Available at: https://www.medicines.org.uk/emc/product/4263/smpc

Version	Date	Amendment	Approved By
1	13/10/2016		Dr Cliona Grant Prof Maccon Keane
2	26/11/2018	Updated to NCCP template Clarification of administration of dacarbazine	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes
Further details on the Cancer Drug Management Programme is available at;
http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/

[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

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.