Bleomycin, Etoposide and CISplatin (BEP) Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Adjuvant treatment of high risk (vascular invasion carcinoma) stage 1 nonseminoma germ cell tumour	C62	00300a	N/A
Metastatic germ cell tumours of the testis	C62	00300b	N/A
Advanced stage or metastatic germ cell tumours (dysgerminoma) of the ovaries	C56	00300c	N/A
Extra-gonadal germ cell tumours	C56/C62	00300d	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 with etoposide and CISplatin is administered on days 1-5, and treatment with bleomycin is administered on days 1, 8 and 15 of a 21 day cycle.

For good risk patients - 3 cycles are administered,
For intermediate to poor risk patients - 4 cycles are administered

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

Admin Order	Day	Drug	Dose	Route	Diluent & Rate
1	1, 8 and 15	[a]Bleomycin	[b]30,000 International Units	IV Bolus or IM[c]	
2	1-5	Etoposide	100mg/m^2	IV infusion	1000mL 0.9% NaCl over 60 minutes[d]
3	1-5	CISplatin	20mg/m^2	IV infusion	1000mL 0.9% NaCl over 60 minutes (Pre hydration therapy required)[e]

[a] Bleomycin dosing should only be expressed in terms of international units.

[b] 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 a cumulative dose of 300,000 international units. Check the cumulative dose prior to each treatment).

[c] For IM injection dose is dissolved in up to 5mL 0.9% NaCl. If pain occurs at the site of injection a 1% solution of lignocaine may be used as a solvent (6).

[d] Hypotension following rapid IV administration has been reported.
Longer infusion times may be required based on the patient's tolerance.

[e] **Prehydration therapy required for CISplatin**
See local hospital policy recommendations.
Suggested prehydration for CISplatin therapy:
Administer 10mmol magnesium sulphate ($MgSO_4$) ((+/-KCl 10-20mmol/L if indicated) in 1000 mL NaCl 0.9% over 60-120 minutes. (Refer to relevant local hospital policy for advice on administration of electrolyte infusions).

Administer CISplatin as described above.

ELIGIBILITY:

- Indications as above
- ECOG status 0-3

CAUTIONS:

- Severe liver impairment

EXCLUSIONS:

- Hypersensitivity to bleomycin, etoposide, CISplatin or any of the excipients.
- Bleomycin is contraindicated in patients with acute pulmonary infection or chest X rays suggesting diffuse fibrotic changes or greatly reduced lung function
- Pre-existing neuropathies ≥ grade 2
- Creatinine clearance < 40 mL/min
- Significant hearing impairment/tinnitus
- Breastfeeding
- Pregnancy

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Pulmonary function tests (PFTs) and chest X-ray prior to bleomycin
- Consider sperm banking for appropriate patients prior to initiation of therapy
- Audiology if clinically indicated

Regular tests:

- FBC weekly during treatment
- Renal and liver profile prior to each treatment cycle
- Chest X-ray prior to each cycle
- PFTs as clinically indicated
- Audiology 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:

- Delay and dose reductions are not recommended as the efficacy of this treatment may be greatly compromised.
- All delays to treatment must be approved by prescribing consultant.
- Prophylactic use of G-CSF is not recommended.
- G-CSF is indicated in patients receiving their second or subsequent cycle of BEP who have had an episode of neutropenic fever or who have not recovered their neutrophil count by Day 5.

Renal and Hepatic Impairment:

Table 1: Dose modifications in renal and hepatic impairment

Drug	Renal impairment		Hepatic Impairment			
Bleomycin	**CrCl (mL/min)**	**Dose**	No need for dose adjustment is expected.			
	>50	No dose adjustment is needed				
	10-50	75% of the original dose				
	<10	50% of the original dose				
	Haemodialysis	50% of the original dose may be considered				
Etoposide	**CrCl (mL/min)**	**Dose**	**Bilirubin (micromol/L)**			**Dose**
	>50	No dose adjustment is needed				
	10-50	75% of the original dose, increase if tolerated	<50	and	Normal albumin and normal renal function	No need for dose adjustment is expected
	Haemodialysis	Not dialysed, consider 75% of the original dose	≥50	or	Decreased albumin levels	Consider 50% of the dose, increase if tolerated
CISplatin	**CrCl (mL/min)**	**Dose**	No need for dose adjustment is expected.			
	50-59	75% of the original dose				
	*40-49	50% of original dose				
	<40	Not recommended				
	Haemodialysis	50% of original dose may be considered				

**Due to the curative intent of this chemotherapy regimen, in cases where CrCl falls between 40-59ml/min it may be appropriate to maintain dose of CISplatin but with extra hydration, longer infusion time and daily Creatinine measurements at the discretion of the prescribing consultant.*

Bleomycin Induced Lung Toxicity:

- Bleomycin can be associated with the development of life-threatening 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:

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

Bleomycin: Minimal **(Refer to local policy)**

Etoposide: Low **(Refer to local policy)**

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

PREMEDICATIONS:

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

OTHER SUPPORTIVE CARE:

No specific recommendations

ADVERSE EFFECTS

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

DRUG INTERACTIONS:

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

REFERENCES:

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Version	Date	Amendment	Approved By
1	08/04/2016		Dr Maccon Keane
2	27/09/2017	Updated with new NCCP regimen template	Prof Maccon Keane
3	06/12/2017	Updated with revised CISplatin	Prof Maccon Keane

		hydration regimen recommendations	
4	20/11/2019	Reviewed. Standardised treatment table and renal dose modifications.	Prof Maccon Keane
5	11/11/2020	Updated baseline tests	Prof Maccon Keane
6	22/10/2021	Removed reference to bleomycin mg dosing. Updated emetogenic potential.	Prof Maccon Keane
7	09/12/2024	Reviewed. Updated pre hydration information for CISplatin in treatment table. Added cautions section. Updated exclusions section. Updated renal and hepatic dose modifications table to align with Giraud et al 2023. Regimen updated in line with NCCP standardisation.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.